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INDEX

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From the Institute of Hygiene and Bacteriology (Head: Gunnar Löfström, M.D., Professor of Bacteriology), University of Uppsala, Sweden, and the Pediatric Department (Head: Bo Vahlquist, M.D., Professor of Pediatrics), University Hospital, Uppsala, Sweden

C-Reactive Protein in Infancy

Its Appearance during the First Year of Life, Transplacental Passage, and Electrophoretic Pattern

by LENNART PHILIPSON and EYVINN TVETERÅS

The presence of C-reactive protein (CRP) in various disorders has been reported by a number of authors (Tillet & Francis 1930, Löfström 1943, Hedlund 1947, and others). Few studies on the occurrence of CRP in infants have been published. Ash (1933) showed it to be present in four infants aged between 6 and 12 months; the diagnoses in these cases were septicaemia, pneumonia, otitis media, and pharyngitis. The titres of non-specific precipitins against pneumococcal fraction C were high in all four instances. Hedlund (1955) later showed that week-old rabbits were capable of producing CRP. Further, Kelly *et al.* (1950) published a report on the occurrence of CRP in a series of infants and children over the age of one year. Gautier & Vest (1956) also studied CRP in infants and children, although no details as to the age of the subjects are given. Very little is known about the appearance of CRP in the newborn and during the first year of life.

A question of primary importance when considering the implications of CRP in the newborn is whether or not the protein passes through the placenta. To the best of our knowledge, no investigations have as yet been made in this sphere. However, Hedlund (1947) has shown that CRP does not occur to any degree in normal pregnancy. On the other hand, Shetlar *et al.* (1955) noted positive CRP tests in apparently uncomplicated pregnancy.

The protein character of CRP was conclusively established by MacLeod & Avery (1941). Its electrophoretic character is as yet not fully clarified. Perlman *et al.* (1943) believed it to migrate as an alpha globulin in moving boundary electrophoresis; at the same time, these authors demonstrated that the specific antibody against C-polysaccharide shows the mobility of a gamma globulin. However, Wood *et al.* (1954) and Hedlund & Brattsten (1955) found in recent studies that C-reactive protein in continuous zone

electrophoresis also moves like a gamma globulin. The latter authors also showed that the protein was distributed evenly over the whole gamma globulin range.

On the basis of animal experiments, Wood (1953) put forward the theory that CRP was a preliminary stage in the formation of antibodies. These studies were made on rabbits, which are capable to produce a protein substance much alike the CRP called C_x-reactive protein. Later investigators claim, however, that CRP is merely a non-specific indicator of disintegration of tissue from bacterial and other origin and that it has no connexion with the production of antibodies. This assumption is corroborated by Good's (1954) studies on the appearance of CRP in agammaglobulinaemia and by Hedlund's (1955) animal experiments on the production of CRP in the young rabbit.

In view of the contradictory records in the literature on the electrophoretic behaviour of CRP, we present in this paper our studies on the electrophoretic pattern of this substance made with zone electrophoresis in vertical columns with a cellulose medium. It appeared to us that it might be of interest to ascertain whether the character of the substance was that of gamma globulin. Our studies embraced a number of pregnancies, to ascertain whether CRP passes through the placenta; also a series of infants, to study the occurrence of CRP during the first year and particularly the first six months of life.

Methods

Electrophoresis.—The zone electrophoresis method in vertical columns with a cellulose medium is described by Porath (in press) and Gedin *et al.* (in press). Pooled CRP-positive serum with a titre of 16 in Löfström's reaction and a titre of + + + + (see below) in the CRP antiserum (CRPA) reaction was used for analysis. The serum was dialyzed before use, 5 ml dialyzed serum being filled into the column in each test. The distribution of proteins is given in terms of their optical density at 2800 Ångström units. Tests for CRP were made both before and after electrophoresis, with both Löfström's and the CRPA reactions. First, individual tubes in the relevant fractions were examined with the CRPA reaction; after evaporation and the addition of calcium ions, the final readings were made with both methods. These tests were made by one of us (Philipson) in collaboration with H. Gedin of the Biochemical Institute of Uppsala, and detailed results will be published in due course.

CRPA reaction.—This test was run as a precipitation reaction in capillary tubes between rabbit antiserum against CRP (Schiefflin) and human serum. The results are expressed as + per millimetre precipitate, the maximum being + + + +. A detailed description of the method will be found in a paper by Anderson & McCarty.

Löfström's reaction.—The method was described by Löfström in 1943. A strain of pneumococci of type 27 was used and the capsular swelling according to Neufeld's technique tested against the sera to be examined. Dilution of the pneumococcal suspensions was proportional to the number of pneumococci, so that titre 1 corresponds

to the lowest concentration, and titre 32 to the highest. Thus, the bacterial density was double four each titre step from 1 to 32. Titre 1 represents 1 to 5 bacteria per field or dilution 1 in 20 of Burroughs and Wellcome's opacity tube No. 3.

Clinical Material

Pregnant Subjects.—Specimens from these patients were supplied by the Gynaecologic and Obstetric Clinic of Uppsala University Hospital. Concurrent specimens were taken from the mother at delivery and from the umbilical blood. Between 5 and 10 ml whole blood were taken. This was allowed to coagulate in the refrigerator for some 12 hours, after which the serum was separated. A sereis of 38 pregnant women was collected from the General Obstetric Wards, to which no patients with acute or specific infections are admitted; and a smaller series of 16 pregnant patients from the Infections Unit of the Obstetric Department, to which patients with acute fever or a history of specific infection are referred.

Infants.—The series was collected from the Pediatric Clinic of Uppsala University Hospital. Blood specimens were taken by finger or heel puncture. In general, blood was taken only from infants in whom the clinical features were suggestive of the presence of CRP. All likely cases in the age group 0 to 6 months were tested. In the age group 6 to 12 months, only occasional specimens were taken. The sera were stored at −20°C until the CRP titre was determined.

Results

A. Electrophoresis.—The results of our electrophoretic studies are given in Fig. 1; positive findings with CRPA are represented by blocked columns, and those with Löfström's test by striped columns. As can be seen in the figure, tubes 36 to 43 yielded positive CRPA titres, those of tubes 37 to 40 being moderately high. A positive Löfström reaction was obtained only in tube 40, the titre being 4. It would appear, then, that the C-reactive protein is intermediate between gamma and beta globulins. To verify the findings, this test was repeated four times with on the whole identical results. Furthermore, paper electrophoresis was also performed from the obtained peaks of the beta and gamma globulin fractions showing that these moved as beta and gamma globulins respectively.

B. Pregnancy.—Table 1 gives the results of the test in the pregnant subjects from the General Obstetric Wards. Of the 38 women in the final stages of pregnancy, the venous blood in 8 gave positive CRPA and Löfström reactions. The titres in these cases never exceeded + + or 4, respectively. In 5 of the 8 cases in which CRP was present, foetal umbilical blood was also tested and was in no instance positive. Only venous blood was obtained from the remaining 3 patients. The incidence of positive CRP tests in the series from the General Obstetric Wards was 21.1 per cent.

Table 2 gives the results of the tests in the pregnant patients from the Infections Unit of the Obstetric Department. It will be seen that in 6 of

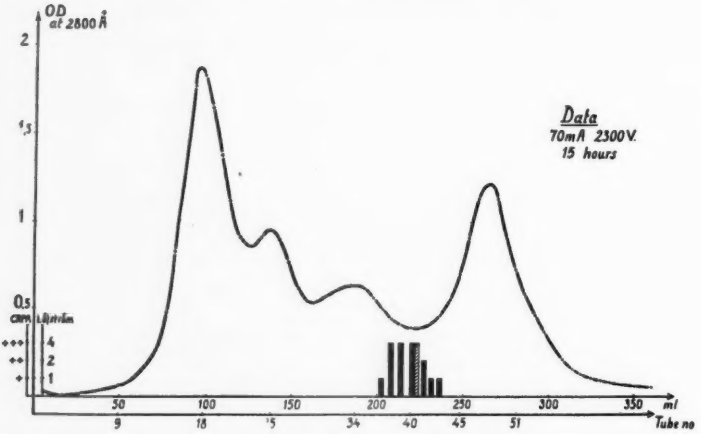

Fig. 1. Electrophoretic pattern of CRP at zone electrophoresis in vertical column.

the 16 cases the venous blood gave positive results, while the umbilical blood was negative. In one of these 6 cases, the CRPA reaction showed a titre of + + + + and Löfström's reaction a titre of 16; in another, the titres were + + + + and 8 respectively. One more case showed titres + + + and 2, while the remaining values did not exceed + + and 4 respectively. Positive CRP tests occurred in 37.5 per cent of the series from the Infections Unit.

TABLE 1

The series from the General Obstetric Wards.

Number of mothers	Venous blood		Umbilical blood		Proportion positive mothers	Mother positive, Umbilical blood neg.
	Pos.	Neg.	Pos.	Neg.		
38	8	30	—	30	21.1 %	5

TABLE 2

The series from the Infections Unit of the Obstetric Department.

Number of mothers	Venous blood		Umbilical blood		Proportion positive mothers	Mother positive, Umbilical blood neg.
	Pos.	Neg.	Pos.	Neg.		
16	6	10	—	16	37.5 %	6

TABLE 3

Nine infants under six months with positive CRP tests.

Case no.	Age	Sex	Diagnosis	Symptoms	CRPA reaction	Löfström reaction	Number of tests during number of days
1	1 day	M	?Intracranial lesion	Somewhat sluggish; whimpered. Moro's embrace reflex negative. Maximum body temperature 38.4°C. Pleocytosis 110/3.2 of which 102 mononuclears.	+ + +(+)	8	3/3
2	6 wks.	M	Congenital megacolon	Usual megacolic symptoms. No fever.			
				Raised ESR, maximum 59 mm, from the age of 4 weeks; cause obscure.	+ + +	8	4/20
3	6 wks.	M	Acute nasopharyngitis	Upper respiratory tract infection with cough for a few days. Maximum fever 38.9°C. Stools somewhat loose. ESR 19 mm.	+ + + +	16	2/3
4	6 wks.	M	Capillary bronchitis	Poor general condition. Highly dyspnoeic. Febrile, temperature over 39°C for several days. ESR 19 mm.	+ + +	4	1
5	8 wks.	M	Multiple skeletal anomalies. Nasopharyngitis	Upper respiratory tract infection for a few days. Body temperature did not exceed 37.5°C. ESR 19 mm. Throat red; nose clogged.	+ +	4	1
6	4 mos.	F	Bronchitic asthma. Acute nasopharyngitis	Upper respiratory tract infection with cough and whistling respiration. Maximum body temperature 37.8°C. Sonorous and sibilant rales. ESR 8 mm.	+ + +	8	1
7	4½ mos.	F	Acute cystopyelitis and meningismus.	Lassitude, coughing, vomiting. No definite clinical signs of meningitis; pleocytosis and pathologically increased protein in the cerebrospinal fluid. Highly febrile; temperature exceeded 40°C. ESR 60 mm. Urine analysis pathological and E. coli in culture.	+ + + +	16	2/3
8	5½ mos.	M	Acute bronchitis plus acute nasopharyngitis	Upper respiratory tract infection with cough and high fever; temperature slightly 39°C for 48 hours. Throat reddened. Bronchitic rale. ESR 25 mm.	+ + + +	8	3/4
9	5½ mos.	M	Bronchitic asthma	Cough, dyspnoea, and lassitude. Body temperature 39°C for 72 hours. Fine and coarse rales. ESR 18 mm.	+ +		2/4

Since 14 women from the General Obstetric Wards and the Infections Unit were found to have positive CRP titres—some in high concentration—and since the foetal specimens were in no instance positive, it would appear that CRP does not pass through the placenta.

C. Infants.—Table 3 gives brief histories of the patients in whom the CRP test was positive. The youngest subject was only one day old, yet showed the highly positive reaction + + +(+) in the CRPA test and 8 in Löfström's reaction on several occasions. The reactions were also markedly positive in 3 subjects aged 6 weeks. A total of 9 infants under the age of 6 months were found to show markedly positive reaction. In all 42 infants in this age range whose clinical appearance suggested positive CRP tests were tested. Thus 33 of the infants showed negative tests. The series is too small to permit any conclusions as to the conditions in which CRP tests are positive. Positive results were obtained in infants between 6 and 12 months in several instances; these cases are not reported in detail since instances of this type are already recorded in the literature and it would appear that the production of CRP at this age is on the whole similar to that of adults.

Discussion

As regards the electrophoretic results, it should be noted that Wood *et al.* (1954) found crystalline CRP in free electrophoresis to show the mobility of a beta globulin, while in zone electrophoresis they found the migration to be suggestive of a gamma globulin. Earlier investigators used starch media in their experiments, whereas we used cellulose media. This might possibly account for the discrepancies between our own observations and the findings of earlier authors who report an even distribution of CRP over the whole gamma globulin range. The results presented in this paper suggest, however, that CRP has an electric rate of movement intermediate between beta and gamma globulins.

Our clinical studies suggest that CRP does not pass through the placenta to the foetus. Like Shetlar *et al.* (1955) we found the CRP titres to be positive in a number of pregnant women. However, our specimens were obtained at delivery, while earlier investigators made their tests during the last trimester of normal pregnancy. It should also be stated that no analysis of the causes of positive CRP tests among the pregnant women was done in this study. Positive tests in pregnancy have not been recorded by other investigators (Hedlund 1947).

Our results show that infants under the age of 6 months are capable of producing CRP. It is of interest to note that this substance, which is thought to be formed in acute stages of bacterial disease, in some acute diseases

accompanied by disintegration of tissue and after the injection of antigens and nonspecific stimulants, is sometimes produced in high concentrations during the first months of life when the production of both gamma globulin and antibodies is defective (Orlandi *et al.* 1955). Our results are corroborated by Hedlund's (1955) experimental studies in the young rabbit. It is as yet too early to assess the diagnostic significance of this early CRP production but the high incidence of negative tests 33 of 42 make it probable that umbilical healing and alike is not the cause of positive CRP tests. This reaction may be of some value since the erythrocyte sedimentation rate and febrile reactions are less valuable as a diagnostic tool during the first six months than later on in life. Furthermore, the test is simple to perform.

Summary

Electrophoretic studies of pooled serum containing CRP with zone electrophoresis in vertical columns with cellulose medium, showed CRP to be intermediate between beta and gamma globulins. A partly selected series of pregnant subjects was tested, the results being positive in 14 of 54 instances. In none of the 11 cases in which the umbilical blood was examined concurrently was the foetal reaction positive, not even when the mother's CRP titre was high. It would appear that this protein is incapable of permeating the placenta. Highly positive CRP titres were found in 9 infants under the age of 6 months. One of these subjects was only one day old. The results suggest that the capacity to form CRP may be present already in early infancy.

Protéine C-réactive (CRP) dans la première enfance.

L'examen de sérum conservé contenant du CRP, au moyen de l'électrophorèse par zone dans des colonnes verticales avec milieu de cellulose, a montré que le CRP se trouve entre les globulines bêta et gamma. Une série restreinte de femmes enceintes a été examinée. Les résultats étaient positifs dans 14 des 54 cas. La réaction était positive dans aucun des 11 cas où le sang du cordon ombilical a été examiné simultanément, même quand le titre de CRP chez la mère était élevé. Il semblerait que cette protéine est incapable de passer le placenta. On a trouvé des taux de CRP très élevés chez neuf nourrissons âgés de moins de six mois. Un de ces sujets n'était âgé que d'un jour. Les résultats suggèrent que la capacité de former du CRP peut exister déjà chez des très jeunes enfants.

C-reaktives Protein (CRP) in der ersten Kindheit.

Die Untersuchung von konserviertem, CRP enthaltendem Serum mit Hilfe von Elektrophorese in Cellulosemilieu hat gezeigt, dass das CRP sich zwischen dem Beta- und Gammaglobulin befindet. Eine kleine Serie gravider Frauen wurde untersucht. Die Resultate waren positiv in 14 von 54 Fällen. Die Reaktion war in keinem der 11 Fälle positiv, bei denen das Nabelstrangsblut gleichzeitig untersucht wurde, selbst dann nicht, wenn der CRP-Titer bei der Mutter erhöht war. Wahrscheinlich hat dieses Protein nicht die Fähigkeit, die Plazenta zu passieren. Bei 9 Säuglingen im Alter von

weniger als 6 Monaten hat man das CRP stark erhöht gefunden. Einer dieser Fällen war nur einen Tag alt. Diese Resultate könnten zeigen, dass die Fähigkeit zur CRP-Bildung schon bei sehr jungen Kindern besteht.

Proteína C-reactiva (CRP) en la primera infancia.

El examen de suero conservado conteniendo CRP mediante la electroforesis en columnas verticales, con un medio de celulosa, ha demostrado que CRP se encuentra entre las globulinas beta y gama. Ha sido examinada una serie reducida de mujeres embarazadas. Los resultados fueron positivos en 14 de los 54 casos. En ninguno de los 11 casos en que la sangre del cordón umbilical fué examinada simultáneamente la reacción no fué positiva, a pesar de que la cantidad de CRP en la madre era elevada. Parece que esta proteína es incapaz de atravesar la placenta. Se han hallado grandes cantidades de CRP en nueve niños de menos de seis meses de edad. Uno de ellos no tenía más que un día. Estos resultados indican que la capacidad de producir CRP puede darse ya en niños de muy tierna edad.

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ADDENDUM

Since the present manuskript was submitted for publication R. Rozansky and B. Bercovici reported a similar investigation on the transplacental passage and appearance during pregnancy of C-reactive protein (C-reactive protein during pregnancy and in cord blood. *Proc. Soc. Exper. Biol. & Med., 92*: 4, 1956).

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From the Pediatric Clinic at Kronprinsessan Lovisas Hospital for Sick Children (Head: C. Gyllenswärd) and Epidemisjukhuset (Head: J. Ström), Stockholm

A Follow-up Study of Children Treated for Acute Purulent Meningitis

by C. G. BERGSTRAND, T. FAHLÉN and A. THILÉN

The introduction of sulfonamides and antibiotics remarkably changed the prognosis of pyogenic meningitis. The mortality which earlier varied between 60 to 100 per cent has been considerably reduced and is stated in some investigations to be less than 10 per cent. At the same time new problems have arisen of which a most important one is to which extent sequelae develop.

It is well known that after treatment with sulfonamides, penicillin and streptomycin serious sequelae appear. No attempt is made here to review the relevant literature; only a few references are given. In a follow-up study of meningococcal meningitis Trolle found an incidence of severe "organic" sequelae of 17 per cent in spite of adequate chemotherapy. Crook *et al.* had in a group of 49 patients with haemophilus influenzae meningitis treated with sulfa, streptomycin and specific antiserum 8 fatal cases and 9 cases with definite residua. Of 90 cases of influenzal meningitis studied by Appelbaum & Nelson severe sequelae developed in 9. In a follow-up study of pneumococcal meningitis (73 cases) treated with penicillin and sulfa, 4 of 29 survivors had defects (Scholtz). Of 281 survivors from purulent meningitis reported by Smith about 16 per cent showed sequelae (cases of tuberculous meningitis excluded), with the highest incidence in the group of pneumococcal meningitis. In two relatively large series of purulent meningitis recently studied by Desmit and by Detmold 16 patients out of 110 and 9 out of 124 respectively presented defects. Some of the patients in these series had been treated with broad-spectrum antibiotics but it is not stated whether the cases with sequelae had received such treatment or not.

To what extent sequelae develop after treatment with broad-spectrum antibiotics has been investigated less intensely. Judging from the reports published, there seems to be a tendency to fewer sequelae in recent years when broad-spectrum antibiotics have been in more general use. Deane *et al.* reported that of 23 cases of pyogenic meningitis, who were treated

with chloramphenicol as the sole form of therapy, 22 recovered completely and one died. A study of influenzal meningitis by Koch & Carson showed a reduction in the incidence of sequelae among the survivors from 20 to 4.3 per cent after the introduction of broad-spectrum antibiotics. In a review of chloramphenicol treatment of influenzal meningitis (Krepler & Leixnering) only 1 case of 82 collected from the literature showed sequelae. Favourable results of treatment with broad-spectrum antibiotics have also been reported in meningococcal meningitis.

The purpose of the present study is to compare the late results of treatment of pyogenic meningitis in two different hospitals in Stockholm during the period 1947–54, with special regard to an impaired vestibular function.

Materials and Methods

The case records at Kronprinsessan Lovisas hospital (K.L.B.) and at the Hospital for Epidemic diseases (Ep.sjh.) for the 8-year period from 1947 through 1954 were reviewed. All patients older than 15 years were excluded. The total number of patients, the distribution of patients according to the various bacterial agents, and the immediate mortality are shown in Table 1. The aetiology was established by isolation of bacteria from the cerebrospinal fluid in 66 cases. The group "unknown" consists of cases with a sterile culture, and the group "miscellaneous" of the few cases where coli, streptococcus and micrococcus catarrhalis were found to be the responsible agent.

Of the 85 surviving patients 70 were reexamined personally. For different reasons 15 did not appear for examination, but since reliable information could be obtained in other ways of 7 of these, it was possible to include them in the study.

In the 70 patients, who appeared for the follow-up study, neurological and vestibular examinations were made. The parents were questioned about the presence of neuro-

TABLE 1

Responsible agent, number of patients and mortality in acute meningitis at Kronprinsessan Lovisas hospital (K.L.B.) and at the Hospital for Epidemic diseases (Ep.sjh.) 1947–1954.

Type of meningitis	K.L.B.		Ep.sjh.	
	Total no.	Deaths	Total no.	Deaths
H. influenzae	12	—	25	—
Meningococcus	4	1	13	—
Pneumococcus	7	—	5	—
Miscellaneous	3	1	0	—
Unknown	11	5	12	—
Total	37	7	55	0

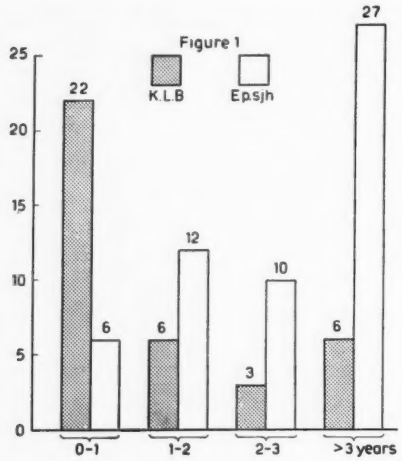

Fig. 1. Age distribution of patients with meningitis at K.L.B. (dotted columns) and at Ep.sjh. (white columns).

logical symptoms, behaviour problems and achievements at school. No detailed psychiatric examination or developmental study was made.

With a few exceptions, the vestibular examination was made during the whole study by the same examiner and included the rotation test and the caloric test.

The age distribution of the patients is shown in Fig. 1.

The treatment during the period studied showed in both hospitals great variations with sulfonamides, penicillin, streptomycin, chloramphenicol and tetracyclins in different combinations. The duration of treatment, too, was variable and an evaluation of the different types of therapy is outside the scope of this study.

The observation period was in no case less than one year.

No patient had been submitted to subdural puncture.

Results

Information was obtained of a total number of 77 surviving patients. Of these 14 had, according to the case records, shown more or less severe defects at the discharge from hospital. At the follow-up 15 patients showed sequelae (Table 2). These patients were evenly distributed over the years 1947 to 1954 and the majority of them (9) had suffered from influenzal meningitis. The sequelae found were mostly of a severe type and are shown in Table 3. As shown by the tables, several patients had more than one defect. The patients were divided in two groups, with and without treatment with streptomycin (Table 4). The number of cases with apparently permanent vestibular damage was 6. In 3 cases there was no previous in-

TABLE 2

Number of reexamined patients and number of patients with sequelae.

Hospital	Average duration of illness before treatment	Total no. of patients	Deaths	Total no. reexamined	Defects
K.L.B.	2.1 days	37	7	27	7
Ep.sjh.	1.6 days	55	0	50	8

TABLE 3

Type of sequelae.

Type of sequelae	No. of patients
Mental retardation . .	5
Hydrocephalus . . .	2
Convulsions	4 (+1)
Paresis	7
Ataxia	3
Deafness	5
Vestibular damage . .	6

TABLE 4

Number of patients treated with and without streptomycin.

Treatment	Total no. of patients	Deaths	Defects	Vestibular damage
With streptomycin	40	1	9	4
Without streptomycin	45	6	5	2

TABLE 5

Number of patients with impaired vestibular function at discharge from hospital and at reexamination.

Treatment	Total no. examined	Impaired vestibular function	
		1st examin.	2nd examin.
With streptomycin	11	6	3
Without streptomycin	6	1	0

formation of the vestibular status nor did these patients know of their defect.

A vestibular examination had been made in 17 patients before they left hospital after the meningitis. According to the case notes, six patients had shown entirely normal vestibular reactions. In four patients the results of the vestibular examinations were somewhat doubtful but could not be definitely stated as abnormal. Seven patients had at this first examination shown signs of impaired vestibular function. Most of them had received treatment with streptomycin (Table 5). At the follow-up examination only 3 of these patients showed definite vestibular damage.

Five patients were mentally retarded, but no other cases with mental defects or with serious behaviour problems attributable to meningitis were found.

Comment

In the present study all the deaths were in the group of patients treated at Kronprinsessan Lovisas Hospital (K.L.B. group). The majority of the patients in this group was under one year of age (Fig. 1) and the observation is in accordance with the recognized fact that mortality in acute septic meningitis is higher in infants than in older children. Probably several causes contribute to the less favourable results in infants. Failure of early clinical diagnosis is generally considered a factor of importance in connection with a fatal outcome in acute meningitis. A different view is, however, held by some authors (e.g. Trolle, Moltke & Raaschou-Nielsen). In this study most of the patients in the K.L.B. group were referred to the hospital with a diagnosis other than acute meningitis, e.g. pneumonia and acute pharyngitis, whereas in the other group nearly all the patients had been diagnosed by the referring doctors as acute meningitis or poliomyelitis. Also, the average duration of illness before institution of treatment was longer in the K.L.B. group (Table 2). If infants only are taken into consideration, the average duration of illness in the K.L.B. group was 2.1 days. The corresponding figure for the Ep.sjh. group was 0.9 days. The observations do not allow of definite conclusions but suggest that a mistake of diagnosis is more often made in infants and that the delay in treatment contributes to a fatal outcome.

Four of the patients who succumbed to meningitis died within 24 hours after admission. Three patients died within four days after the diagnosis had been made.

The difference between the number of patients with sequelae at discharge (14) and at reexamination (15) is due to the fact that three patients had

recovered completely at the time of reexamination and four patients showed signs of impaired vestibular function which had not been detected at discharge from hospital.

The average duration of illness before institution of treatment was in the cases with sequelae 2.2 days. This figure does not significantly differ from the average figure for the total K.L.B. group but is higher than the corresponding figure for the total Ep.sjh. group (Table 2). It seems hardly safe to draw any conclusions from these observations.

Six patients showed at the reexamination signs of permanently impaired vestibular function. Two of these patients had not received treatment with streptomycin in any form. Their vestibular lesions were unilateral. Of the four patients with streptomycin all had been treated for more than 24 hours and in all patients streptomycin had in addition been administered intrathecally. In one of them the lesion was unilateral.

It is recognized that the intrathecal route of administration greatly increases the danger of treatment with streptomycin (Appelbaum & Nelson, Alexander). It is of interest to note that streptomycin was given intrathecally to 10 patients without serious complications.

Of the 6 patients treated with streptomycin and known to have had signs of impaired vestibular function at discharge from hospital three showed such signs at the reexamination (Table 5). Two patients had normal vestibular reactions and one patient who could not be reexamined was, according to the parents, in perfect health. Of the three patients with positive findings one showed a unilateral vestibular lesion. It is most likely that in this case the vestibular damage was not caused by the treatment with streptomycin but was a complication of the meningitis as such. The same is possibly true of the patients who had normal vestibular reactions at reexamination. It has, however, been shown (Moffitt & Norman) that even severe vestibular depression caused by streptomycin may be reversible, and for this reason no definite conclusions can be drawn.

The present study has confirmed that vestibular damage may occur in patients with pyogenic meningitis treated without streptomycin and that, at least in some cases, this damage is reversible. It is possible that transient vestibular damage is not an uncommon complication of septic meningitis, and it would be of interest to follow a larger number of patients than that reported in the present study.

Summary

A Follow-up Study of Children Treated for Acute Purulent Meningitis.

A follow-up study was made of 92 children with acute septic menigitis treated in two different hospitals in Stockholm during the period 1947–1954. There were seven

deaths during this period. Information concerning 77 of the survivors could be obtained. Of these 15 had more or less severe sequelae. Six patients showed impaired vestibular function at reexamination. Seven patients (6 treated with streptomycin) were known to have had impaired vestibular function at discharge from hospital. Of these three had abnormal vestibular reactions at reexamination.

Recherches poursuivies chez des enfants traités pour méningite purulente aiguë.

Des recherches poursuivies ont été faites en deux hôpitaux de Stockholm, chez 92 enfants atteints de méningite purulente aigüe pendant la période 1947–1954. Il y a eu 7 décès durant cette période. On a pu obtenir des informations quant à 77 des survivants. 15 permi eux souffraient de séquelles plus ou moins graves. Six malades présentaient au réexamen des troubles de la fonction vestibulaire. On a su que 7 autres (6 traités par la streptomycine) avaient eu des troubles de la fonction vestibulaire après avoir quitté l'hôpital. 3 sur ces 6 ont présenté des réactions vestibulaires anormales lors d'un réexamen.

Eine Nachuntersuchung wegen akuter purulenter Meningitis behandelter Kinder.

Es wurden 92 Kinder mit akuter septischer Meningitis, die in der Periode 1947–1954 in zwei Krankenhäusern in Stockholm behandelt waren, nachuntersucht. In diesem Zeitraum traten sieben Todesfälle auf. Es konnten Einzelheiten eingeholt werden über 77 Überlebenden, und von diesen hatten 15 mehr oder weniger ernste Folgen. Die nochmalige Untersuchung ergab bei sechs Patienten vestibuläre Funktionsstörungen. Es war bekannt, dass 7 Patienten (von denen 6 mit Streptomycin behandelt worden waren) zur Zeit der Entlassung aus dem Krankenhaus gleiche Beschwerden aufwiesen. Bei der im Rahmen der Nachuntersuchung vorgenommenen körperlichen Untersuchung konnten bei drei dieser 7 Patienten abnorme vestibuläre Reaktionen festgestellt werden.

Estudio proseguido del tratamiento de niños enfermos de meningitis purulenta aguda.

El estudio de 92 casos de meningitis séptica infantil aguda, tratados en dos hospitales distintos, se prosiguió durante el período 1947–1954, en Estocolmo. Fallecieron 7 casos durante dicho plazo. Pudo obtenerse información referente a los 77 sobrevivientes, en 15 de los cuales se manifestaron secuelas más o menos graves, en 6 de ellos se mostró defectuosa la función vestibular una vez examinados, y en 7 pacientes (6 tratados con estreptomicina) se sabía la función vestibular defectuosa al despedírseles del hospital. De éstos, 3 manifestaron reacciones vestibulares anormales cuando se les volvió a examinar.

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DOSERING

Spädbarn och småbarn: 20 mg per kg kroppsvikt och dygn. Ges lämpligen efter en lätt måltid eller ett glas mjölk, och medföljande måttsked användes.

Under 1 år	1/4 — 1/2 sked × 4
1 — 5 år	1/2 — 1 sked × 3 — 4
6 — 10 år	1 sked × 4 — 5
11 — 15 år	2 skedar × 3 — 4
Vuxna	2 skedar × 4

FÖRPACKNING

Glas à 60 ml, innehållande 1,5 g Terramycin, med doseringssked.

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Medföljer som tidningsbilaga

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Myalgia Cruris Epidemica

by ÅKE LUNDBERG

In the spring of 1955, an illness was observed in Stockholm with practically identical clinical features in every case. Those affected were mainly children, often in the same school class or the same family. The onset was acute, with high fever and prodromal symptoms in the form of headache and slight catarrhal manifestations. The fever lasted for about four days, the prodromal symptoms for not quite as long. When these had subsided, and the fever was in the final stage, such severe pain appeared in the calf muscles that many of the patients were unable to walk. The maximum of the pain coincided with the return of the temperature to normal. The pain lasted for about three days, after which the patients were completely asymptomatic, the duration of the entire illness being a bare week.

A few years ago, Ström (12) observed a similar condition in some children in one school class. In addition to the cases occurring in Stockholm in the spring of 1955, cases of the same nature were reported by colleagues in other parts of the country during the same period. I have been unable to find any corresponding reports in the literature.

Localized muscle pain occurring epidemically has been known since the middle of the 19th century, when the first cases of Bornholm disease (synonyms: epidemic pleurodynia, epidemic myalgia, Bamle disease) were reported from Iceland. A detailed study was published in 1933 by Sylvest (13). In this disease, the muscle pain is localized to the lower part of the chest and the upper part of the abdomen.

In 1947, Ström published his first report on myalgia nuchae epidemica, a disease first described by Massel and Solomon in the U.S.A. An account of nine cases of myalgia coxae was given by Hermansson in 1950.

Present Investigation

Case Material

The *case material* consisted of 74 cases of myalgia of the calf (Table 1). Eleven patients were admitted to Kronprinsessan Lovisas Barnsjukhus, 5

TABLE 1

Cases with myalgia of the calf only.

Category		Number of cases		
		♂	♀	Total
In-patients	Kronprinsessan Lovisas Barnsjukhus . . .	10	1	11
	Paediatric Clinic, Karolinska Sjukhuset . .	4	1	5
	Stockholm Hospital for Contagious Diseases	2	0	2
Out-patients: Kronprinsessan Lovisas Barnsjukhus . .		18	17	35
Telephoned history		13	8	21
Total		47	27	74

to the Paediatric Clinic of Karolinska Sjukhuset, and 2 to the Stockholm Hospital for Contagious Diseases. Examination was made at the out-patient department of Kronprinsessan Lovisas Barnsjukhus in 35 cases. In 21 cases the history was taken by telephone, since the children had already recovered when I contacted the parents, who were unwilling to take the trouble of bringing the children to hospital for examination. The *sex distribution* showed a preponderance of males. This was particularly marked in the in-patients (16 males and 2 females), who represented the severest cases.

I was also able to contact patients who, after similar prodromal symptoms, suffered from myalgia, but at another site than the calves (Table 2). In 4 cases there was myalgia of the neck, and in 9 cases the patients complained of pain in the thigh muscles; one patient had pain both in the neck and in the back of the thigh. It is of interest to note that several of these patients belonged to families in which other members had suffered from myalgia of the calf, or subsequently contracted it.

TABLE 2

Cases with myalgia at another site than the calf.

Site of myalgia		Number of cases		
		♂	♀	Total
Neck		1	3	4
Thigh	Back	1	0	1
	Front	1	3	4
	Indefinite . . .	0	4	4
Both neck and thigh . .		0	1	1
Total		3	11	14

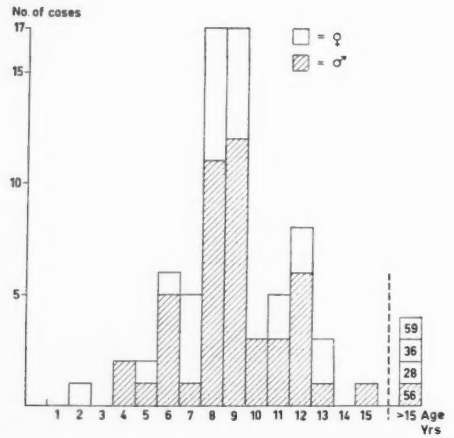

Fig. 1. Age distribution of the patients with myalgia of the calf (74 cases).

The *age distribution* of the cases of calf myalgia is shown in Fig. 1. Four patients were over 15 years old; the respective ages are noted in the columns. Children of elementary-school age predominated; these Stockholm schools were, in fact, systematically investigated. It is true that younger children cannot give exact information about their symptoms, but if the parents notice that they have difficulty in walking in connexion with an acute febrile illness, this usually leads nowadays to rapid contact with a physician, and thence in most cases with a hospital. Consequently, this age group can also be regarded as fairly adequately represented. Had there been any considerable number of cases in the higher age groups, the hospitals for contagious

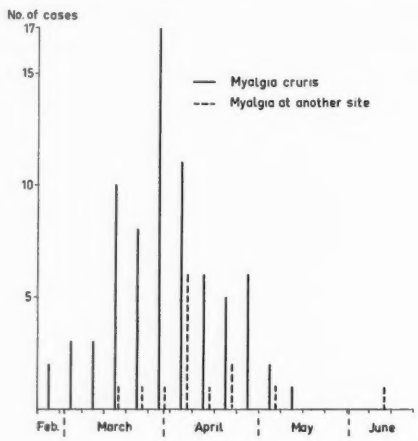

Fig. 2. Seasonal distribution.

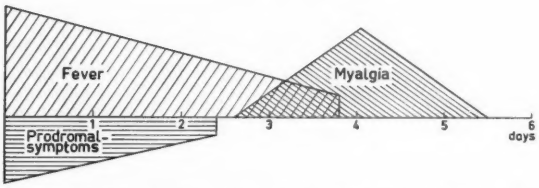

Fig. 3. Course of illness in patients with myalgia of the calf.

Duration of fever	3.8 days
Duration of prodromal symptoms	2.4
Onset of calf pain	2.6
Duration of calf pain	2.9

diseases could be expected to have been in contact with these patients. No adult with this illness was admitted to the Stockholm Hospital for Contagious Diseases. These facts indicate that the figures given lie close to the real figures. The mean age was 9 years.

The *seasonal distribution* (Fig. 2) shows a definite accumulation from the middle of March to the end of April, with a peak at the turn of the month. No definite case of calf myalgia was observed earlier than February or later than May. The cases of myalgia at another site are also recorded in the figure; they show a similar time distribution.

Clinical Features

The *course of the illness* is recorded schematically in Fig. 3. The onset was acute, with high fever and prodromal symptoms, consisting of headache and slight catarrhal symptoms. The duration of fever was about four days, and that of the prodromal symptoms not fully as long. When these had subsided, and the fever had almost gone down, the calf pain started and reached its maximum when the patient became afebrile. After about three days' pain, the patients were entirely asymptomatic.

The *symptoms and signs* are recorded in Fig. 4. Fever was present in 92 per cent of the cases. Particularly in the children, it was initially high, i.e., about 39 to 40°C. Headache was complained of by about 80 per cent. A cough and rhinitis were present in almost half the patients, and a few complained of a sore throat.

Nausea and vomiting appeared in 41 per cent of the cases; only a few patients had diarrhoea.

Pain in the muscles of both calves was present in 92 per cent of the cases. It was not possible to establish any definite predilection for the right or the left side.

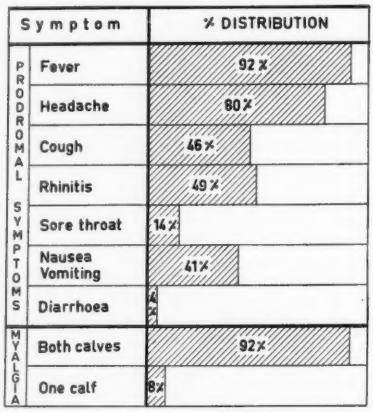

Fig. 4. Symptoms and signs in patients with myalgia of the calf.

The *muscle pain* was so severe in many cases that difficulty was found in walking. Statements that a child had to be carried to the toilet, or could possibly creep to it, were common. In a village outside Uppsala, the illness was called, characteristically enough, "the creeping sickness" by the parents of the affected children (14).

In most cases, the pain was localized to the upper, fleshy part of the calf, often laterally, and was deep seated. It was in the nature of a dull ache, like muscle strain; a few of the older boys stated that it was exactly like the soreness following strenuous exercise.

The patients had no discomfort at rest, the pain being brought on only by movement. If the patients were able to walk at all, they found it least painful to walk on tiptoe.

Inspection of the calf showed nothing abnormal, and no swelling was present. On palpation, there was tenderness in a circumscribed area of the fleshiest part of the calf. Slightly increased muscular tonus was often found.

The *gait* was jerky, uncertain and wide-stepped. The patients preferred to walk on tiptoe, with bent knees. It seemed as if stretching of the muscles was considerably more painful than active contraction, a feature that has also been observed in Bornholm disease with intercostal myalgia (13). The explanation is presumably to be sought in a state of contraction in the muscle involved.

Apart from the disturbance in gait, and a faintly positive Lasègue sign in three children, the neurologic status was normal; no paresis was observed.

A specimen of the affected muscle was taken for *biopsy* in two cases. Examination (Dr. B. Ivemark, Karolinska Sjukhuset) showed unspecific, degenerative changes in both cases.

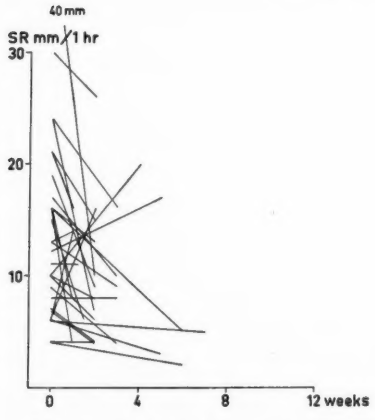

Fig. 5. Sedimentation rate during acute stage of myalgia of the calf and at follow-up examination (29 patients).

Electromyographic recordings were made in three cases (Dr. L. Widén, Serafimerlasarettet): nothing pathologic was found.

The *electrocardiogram* was recorded in 13 cases during the acute stage; all the tracings lay within the normal range of variation.

Electroencephalograms were recorded in 16 patients. Normal tracings were present in 6. In 3 cases reversible changes were recorded which could have been in accordance with encephalitis. In the remaining 7 cases, unspecific dysrhythmia was noted; in 2 of them it persisted at a follow-up examination.

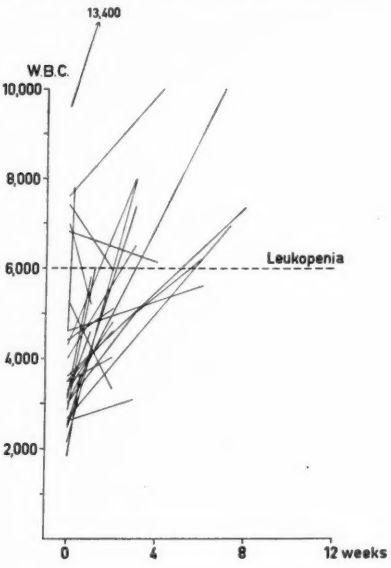

Fig. 6. White blood cell count during acute stage of myalgia of the calf and at follow-up examination (25 patients).

Lumbar puncture was done in 17 patients. In none of them was there any increase in the cell count of the cerebrospinal fluid. The total protein content was normal in all 10 cases in which it was determined.

The urine of two children was analyzed for the presence of *myoglobin* (Docent B. Josephson, S:t Eriks Sjukhus); the results were negative.

The *sedimentation rate* was determined in 29 patients during the acute stage, as well as some time afterwards; in Fig. 5, these two values are joined by a straight line. A moderate rise was present, but the tendency to normalization was evident.

The *white blood cell count* was determined in 25 patients at the beginning of the illness and after recovery; the two values are joined by a straight line in Fig. 6. The borderline for leukopenia has been drawn at 6000 (5). The tendency to leukopenia as well as the subsequent normalization are apparent.

A *differential white cell count* showed relative lymphocytosis in half of the cases; in 6 of the 23 examined there was a moderate shift to the left.

The *thymol turbidity* test was normal in the 6 children in whom it was made.

Three earlier *neotuberculin-positive* children did not react during the illness, but once more showed a positive reaction about a week after recovery. In 4 children the tuberculin reaction was unaffected by the illness.

Epidemiologic Data

The distribution of the cases in the City of Stockholm is shown on the map (Fig. 7). It is no coincidence that half of the cases are found in the southern suburbs; of the 70,000 elementary school children in Stockholm, 35,000 belong to this area. There is no significant difference between the various residential districts with respect to the time of onset of the illness. Families and school classes were of particular interest, since they afforded the best possibilities of tracing contacts.

Kungsholm's elementary school has 2433 pupils. As far as could be ascertained, 9 of them contracted calf myalgia. The circumstances in these cases are shown in Fig. 8. The figure in the symbol representing each child denotes the age in years. The three children in family B are accounted for in the left part of the figure; they fell ill at intervals of two days in each case. The 6-year-old boy did not go to school, the other two sibs each attended a separate division of Kungsholm's elementary school, which is shown in the right half of the figure. The two divisions are about 1 kilometer apart; one building is on Garvargatan and one on Mariebergsgatan. The B sibs were the first in the school to fall ill. The 8-year-old boy was a classmate of the children in the division on Garvargatan. Seven days after he fell ill, the next case occurred, followed 5 days later by a further case. Thirteen days

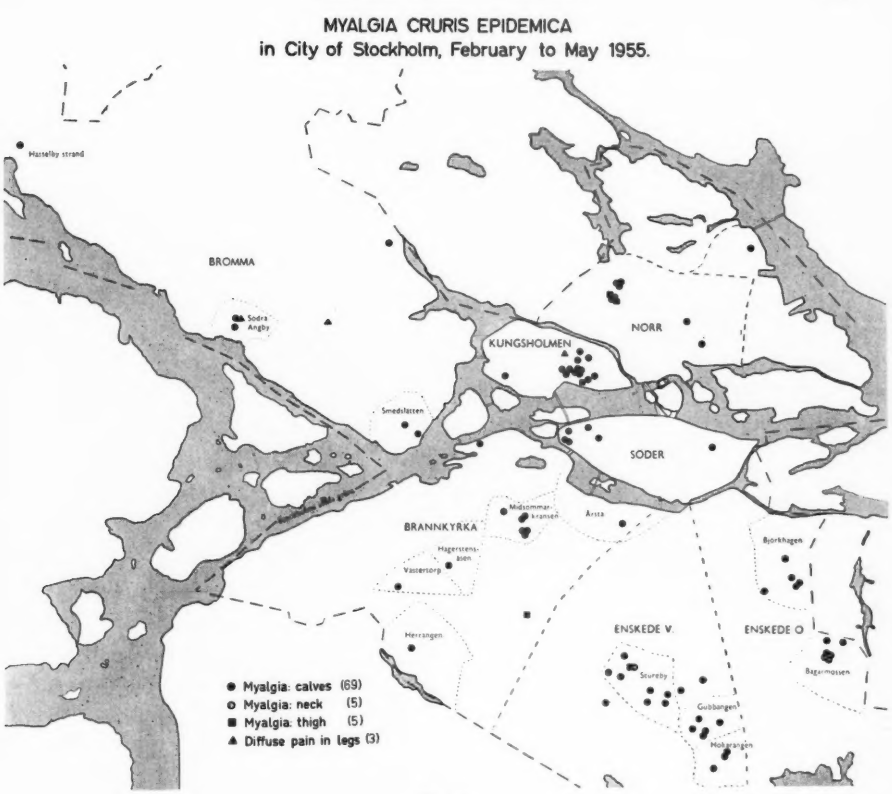

Fig. 7.

later, myalgia developed in still another classmate, but in this case the pain was located in the thighs. The 13-year-old girl in family B attended the other division of the school, but was not in the same class as the four classmates who fell ill within a few days of each other. A 12-year-old boy in another class contracted the illness during the same period. The youngest B sib (who did not attend school) was a playmate of the 10-year-old boy who was the second in class 3 to fall ill, and lived in the same part of the apartment house as he did.

I contacted the parents of all the children in class 3 by telephone. Of the 30 children in the class, 4 had contracted myalgia of the calf in the course of 8 days (see Fig. 8). During this time, 6 other children had been kept at home on account of "influenza". Closer questioning elicited the fact that two of them had pain in the legs, although it could not definitely be localized to the calves.

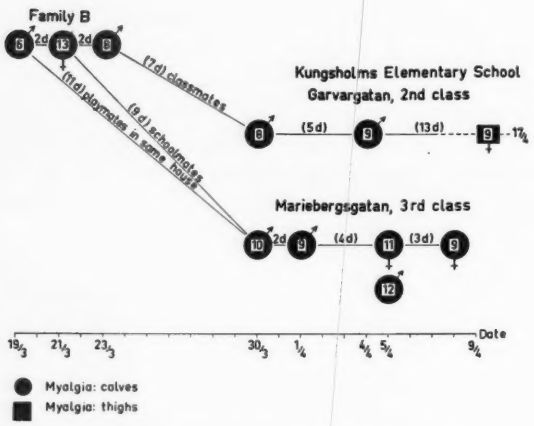

Fig 8. Cases in Kungsholm's Elementary School. (The figure in each symbol denotes the age. The bracketed figures denote the interval between the onset in the cases joined by a line.)

Some cases of myalgia of the calves and myalgia of the neck in the same neighbourhood are recorded in Fig. 9.

Bagarmossen's elementary school has 753 pupils; 3 of the boys are known to have contracted myalgia of the calf. Two of the boys lived close to each other on the same street. Seven days after one of the boys fell ill, typical myalgia of the neck with the clinical features described by Ström (11) appeared in the other members of the family (father, mother and 3-year-old sister). The other boy's parents became ill three weeks after him, with a short, influenza-like illness. A day or so afterwards, they went to stay with friends in Oskarshamn (about 400 km from Stockholm). One week later, the mother and a 3-year-old son in this family fell ill with typical myalgia of the calf, and two other members of the family had "influenza" without muscular pain.

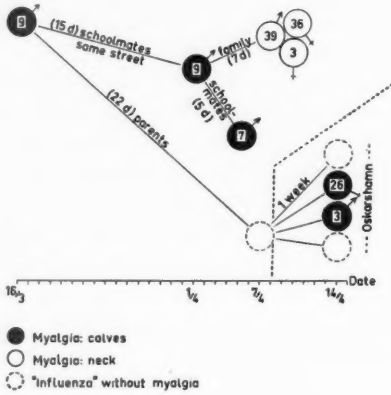

Fig. 9. Cases of myalgia of the calf and myalgia of the neck in the same neighbourhood. (For explanation of numbers, see Fig. 8.)

At Kronprinsessan Lovisas Barnsjukhus, three cases of myalgia of the calf were treated in one ward from March 16 to 26. On April 2, a nurse contracted the same illness; no other secondary cases were observed. The affected children had been isolated.

In three cases there was a recurrence of the illness, two to six weeks after the first attack. The second attack was mild in every case.

A few children complained of diffuse leg pains for a few weeks after the illness, particularly on exertion, such as football or cycling.

The *incubation period* ranged from about 2 to 10 days.

Virologic investigations of samples from the throat, blood and faeces were made at the State Bacteriological Laboratory. Whenever possible, samples were also taken two weeks after recovery. Samples from unaffected members of the families were taken as well. The final results have not yet been obtained.

Therapy and Prognosis

Since the aetiology was unknown, *therapy* was purely symptomatic, i.e., analgetics, local application of heat, and rest.

In all the cases observed in the present investigation, the *prognosis* was entirely good.

Discussion

Differential Diagnosis

Difficulties were encountered in establishing the diagnosis until it became evident, through the appearance of a number of similar cases, that a well-defined symptom complex was present. The acute onset with fever and headache, as well as the subsequent muscular pain, were reminiscent of *aparalytic poliomyelitis*. The diphasic course is characteristic of both conditions, but the recurrence of fever with the onset of pain is lacking in myalgia of the calf. No neck rigidity was observed, and the findings in the cerebrospinal fluid were normal.

An element of *encephalitis* cannot be ruled out entirely, even if it can scarcely have been marked. Somnolence and convulsions were lacking, but the EEG was pathologic in 3 of the 16 patients in which it was recorded during the illness, whereas the tracings made after recovery were normal.

Polyradiculitis of the Guillain–Barré type is often associated with paresis, loss of sensitivity and an increase in the protein content of the cerebrospinal fluid. In mild radiculitis these symptoms may, however, be inappreciable or absent (1, 11).

Fog (1953) described 10 cases of "*neuritis vegetativa (epidemica?)*", all the patients being women about 30 years of age. Signs of peripheral circula-

tory disturbances were present, the muscular pains had no definite localization, and the illness lasted for weeks or even months.

Myoglobin could not be demonstrated in the urine of the two patients in which it was investigated. The colour of the urine was normal in all the patients. Consequently, the illness could not have been the *myoglobinuria* with calf pain described by Hed.

The site of the muscular pain makes the illness easy to differentiate from earlier described localized myalgia, i.e., *Bornholm disease* (13, 9), *myalgia nuchae epidemica* (11), and *myalgia coxae* (8).

The question arises whether the illness can have been *influenza*. The onset is in fairly good agreement, but such distinct and localized myalgia coinciding as to time and place is not encountered in the illness commonly known as influenza. Moreover, no certain case of influenza was observed in Stockholm during the spring of 1955 (12).

Aetiology

The infectious background of myalgia of the calf can be regarded as certain. The nature of the prodromal symptoms and the accumulation of cases in families and schools during a limited period of time afford strong evidence of this fact.

Whether the invading organism is of bacterial or of viral origin is not known. The presence of leukopenia and the moderately raised sedimentation rate are possible indications that a virus is the responsible organism.

The presence of the Coxsackie virus has been demonstrated in Bornholm disease (4, 9). No case of this disease was observed in the vicinity of cases of myalgia of the calf. A noteworthy fact is that cases of myalgia of the neck occurred concurrently in families in which other members had suffered from myalgia of the calf. In the series of myalgia of the neck reported by STRÖM, the Coxsackie virus was recovered in none of the cases (9).

Pathogenesis

Radiculitis has been stressed by several authors as a possible source of muscular pain in certain infectious diseases. Ström (11) entered into a detailed discussion of the pathogenesis in myalgia of the neck, and concluded that "the disease is a polyradiculitis, particularly within the cervical segments", and therefore named it "polyradiculitis cervicalis infectiosa" in his most recent report. Bendz expressed the view that "the source of pain associated with acute poliomyelitis is to be sought in the nerve roots".

The type of muscular pain occurring in myalgia of the calf exhibits similarities to the pain in the aforementioned diseases. The occurrence of cases of myalgia of the neck and myalgia of the calf in the same families should also

be borne in mind. It must nevertheless be pointed out that myalgia of the neck mainly affects adults. In addition, the diphasic course is lacking, and the findings at examination of a biopsy specimen of the muscle are negative.

The question then arises whether any feature of myalgia of the calf argues against radiculitis as the origin.

A remarkable fact is that a positive Lasègue sign was present in only three patients, and was then somewhat doubtful.

A low cellular–high protein content of the cerebrospinal fluid is not an obligatory feature in polyradiculitis (1). The rise in the protein content does not reach a maximum until about a week after the onset. Examination of the cerebrospinal fluid was not made in any of the cases of myalgia of the calf later than four days after the onset.

The fortunately good prognosis of the illness in question prevented any direct histological study of the nerve roots. The question of nerve root involvement as the origin of myalgia of the calf must therefore be left open, although at the present stage radiculitis appears to be the most likely pathogenetic explanation.

Can the symptoms be explained by a localized, inflammatory process in the muscle, i.e., myositis? It is possible, but in this event it is remarkable that neither swelling, redness nor fluctuation was observed in any of the cases, and that the site of tenderness was circumscribed, and had not spread to an entire group of muscles.

Why were the calf muscles in particular the site of pain? The great majority of patients were children, and they run more than do adults. There was a predominance of boys, and they exercise their legs more than girls do. The history strikingly often showed a statement of unusually strenuous skiing, football or skipping shortly before the onset of the illness. Moreover, the discomfort was said to resemble that of soreness after strenuous exercise. That overexertion plays a role in producing pain in the involved muscles is known from observations in poliomyelitis, polyradiculitis (1) and Bornholm disease (10), as well as in the myoglobinuria with calf pain described by Hed.

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I am greatly indebted to Dr. Urban Hjärne, Chief Elementary School Physician, for the collection of the case material. On his instructions, a circular was sent to the school nurses at all the elementary schools in the City of Stockholm, asking them to notify me of every suspected case of myalgia of the calf.

Professor Arvid Wallgren, Head of the Paediatric Clinic of Karolinska Sjukhuset, was kind enough to allow me access to the case records of the children admitted there, and to use information from these records for the present investigation.

My colleagues at Sachs' Hospital for Children and Samariten Children's Hospital kindly informed me of their observations.

Summary

A contagious disease not earlier described in the literature appeared during a limited period in the spring of 1955. The majority of patients were children.

The incubation period ranged from about 2 to 10 days. The onset was associated with high fever and headache. When the temperature had almost returned to normal, and the headache had subsided, usually after three to four days, pain developed in the calf muscles. In many cases it was so severe that the patient was unable to walk. After a further three days, the myalgia disappeared.

Apart from a disturbance in gait, probably caused by the pain, nothing abnormal was observed in the neurologic status. The findings in the cerebrospinal fluid were normal. In the cases observed, altogether 74 in Stockholm, the prognosis was good.

Since the aetiology is as yet unknown, the purely descriptive designation myalgia cruris epidemica is suggested for the illness in question.

Myalgie epidémique de la jambe.

Une maladie contagieuse non encore décrite par la bibliographie s'est manifestée pendant une période du printemps de 1955. La plupart des malades étaient des enfants. La période d'incubation comportait 2 à 10 jours. L'attaque était accompagnée de forte fièvre et de maux de tête. Quand la température avait presque repris la normale et que les maux de tête avaient cessé, en général après 3–4 jours, il survenait des douleurs dans les muscles du mollet. Ces doulerus ont été si fortes en plusieurs cas que le malade était incapable de marcher. Trois jours plus tard encore, la myalgie avait disparu. Sauf un trouble de la démarche, probablement causé par la douleur, le status neurologique n'a pas révélé rien d'anormal. Le liquide cérébro-spinal était normal. Le pronostic des cas observés, 74 en tout à Stockholm, était bon. L'étiologie étant encore inconnue, l'auteur suggère de présenter cette maladie de façon purement descriptive comme myalgie de la jambe.

Myalgia cruris epidemica.

Im Frühjahr 1955 trat während einer kurzen Periode eine kontagiöse Krankheit auf, die bis dahin noch nicht in der Literatur beschrieben war. Es wurden hauptsächlich Kinder befallen. Die Inkubationszeit schwankte von ca. 2 bis 10 Tagen. Der Ausbruch der Krankheit ging mit hohem Fieber und Kopfschmerzen einher. Nachdem die Temperatur wiederum beinahe normal war, und die Kopfschmerzen nachgelassen hatten, gewöhnlich nach 3–4 Tagen, entwickelten sich in den Wadenmuskeln Schmerzen. In vielen Fällen waren die Schmerzen so stark, dass der Patient nicht gehen konnte. Nach weiteren drei Tagen verschwand die Myalgie. Es konnte bei der neurologischen Untersuchnung, mit Aushnahme einer wahrscheinlich durch die Schmerzen verursachten Störung beim Gehen, nichts Abnormes beobachtet werden. Die Ergebnisse der Untersuchung der Cerebrospinalflüssigkeit waren normal. Die Prognose war in den untersuchten Fällen, in Stockholm insgesamt 74, gut. Da die Ätiologie bis jetzt unbekannt ist, wird vorgeschlagen, die in Frage kommende Krankheit als Myalgia cruris zu bezeichnen.

Mialgia cruris epidémica.

Una enfermedad contagiosa, no descrita anteriormente en la literatura, apareció durante un período limitado, en la primavera de 1955. La mayoría de los pacientes fue-

ron niños. El plazo de incubación varió de 2 a 10 días. El ataque estaba acompañado con elevada calentura y dolor de cabeza. Al volver la temperatura casi a la normalidad y remitirse el dolor de cabeza, habitualmente después de 3 a 4 días, se desarrollaba un dolor en los músculos de la pantorrilla. En muchos casos era tan fuerte que el paciente no podía andar. Transcurridos otros tres días, desaparecía la mialgia. Aparte de una perturbación de la marcha, causada probablemente por el dolor, no se observó nada anormal en el status neurológico. Tampoco se descubrió nada anormal en el líquido céfallorraguídeo. En los casos observados, en total 74, en Estocolmo, el pronóstico fué bueno. Como se ignora todavía la etiología de esta afección, se sugiere sencillamente la denominación descriptiva de Mialgia cruris para designarla.

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Children under Stress in a Pediatric Clinic

A Study Concerning the Relationship between Somatic Complaints and Emotional Disturbances as Observed in a Temporary Shelter[1]

by WILFRED C. HULSE, WILLIAM S. DAVIS and H. MICHAL-SMITH

Clinical Study

The material for this study is derived from a research project on psychogenic factors in the development of physical complaints as seen in a child care institution. The purpose of this paper is to demonstrate the extent to which psychogenic factors cause visits to the pediatric clinic, located at the Children's Center, Department of Welfare, City of New York. This institution is a non-sectarian, inter-racial, publically operated temporary shelter for dependent and neglected children between the ages of two and sixteen years and with a rated capacity of 356 children. The annual population turnover is approximately 1780 children. Because of difficulties in securing appropriate foster care nearly two-thirds of the children in residence remain beyond a period of temporary care; some for as long as two and three years (3, 4). The orthopsychiatric personnel at Children's Center consist of a consulting psychiatrist, a chief psychiatrist and an associate psychiatrist, a director of Social Service, seven psychiatric caseworkers, a consulting psychologist, two staff psychologists and three psychological internes. The medical care is under the direction of the Department of Pediatrics, New York Medical College, Flower-Fifth Avenue Hospital. A resident infirmary is in operation for those children with short periods of illness who are not considered sick enough for hospitalization.

A psychosomatic questionnaire was formulated to facilitate the recording of psychogenic as well as physical factors involved in medical visits by

[1] The authors are indebted to Miss Florence Ausubel, Statistician, and Miss Jean Fenmore, Children's Counselor, without whose help and devoted collaboration this study could not have been carried out.

the children at the Center. The questionnaire used in this study consists of three main subdivisions: The first, "Information", includes name, sex, age, dormitory designation, time of visits, source of referral and source of complaint. The second subdivision, "Observation", includes physical findings, a description of behavior and a checklist of behavior manifestations. The third subdivision, "Conclusion", includes clinical diagnosis, behavioral diagnosis, treatment and disposition.

During the period from July 1, 1951 through January 31, 1952 a psychosomatic questionnaire was completed for each visit or repeat visit of a school age child to the clinic and/or infirmary which also serves as an emergency clinic after clinic hours. Clinic visits were made for diagnostic and therapeutic purposes, routine physical checkups, immunizations, admission to the infirmary or referral to other clinics or hospitals. Each counselor or teacher in the institution can send a child to the clinic. Children can also come on their own initiative. The resident pediatrician or the nurse in attendance are responsible for the completion of the questionnaire.

In all there were 5793 visits made by 610 different school age children during the research period. Since there were 867 different school age children at Children's Center for longer and shorter periods during the seven months of research, 257 children never visited the clinic. The 610 children who visited the clinic constitute 70.4 per cent of the total number of children in residence. There were 91 children who made 20 or more visits to the clinic. These 91 cases represented 10.5 per cent of the resident population and involved 2945 visits, i.e., 51 per cent of the total number of visits. In short, 10.5 per cent of all the children in residence accounted for 51.7 per cent, more than half of all the visits. The four children who were the most frequent visitors made 94, 69, 54 and 53 visits respectively to the clinic.

The questionnaire permitted to categorize the clinic visits into two groups, "legitimate" and "questionable". The legitimacy of visits was determined by the examining doctor or nurse through the establishment of physical findings warranting medical care, such as temperature, cold congestion, physical injuries, etc. In the absence of physical findings such complaints as headaches, stomach aches and muscle pains were considered legitimate if the observed behavior was in accordance with the complaint.

In all cases the physician or nurse had to explain on the questionnaire if and why the visit was not considered legitimate. In these cases the application of a "placebo" was permitted if such treatment was considered helpful for psychological reasons. Return visits were allowed in all cases.

Out of the 25 cases with the highest number of clinic visits 15 were investigated by intensive psychological and psychiatric analysis. The other 10 who made up this group had to be eliminated because they had been dis-

charged before case material could be evaluated or were for other reasons inaccessible for psychiatric investigation.

The psychological and psychiatric investigation of these fifteen cases indicated severe emotional disturbances in all of them. Thirteen children showed psychoneurotic disorders, early neurotic character formation or primary behavior disorders with anxiety state (actual neurosis). The remaining two children were borderline psychotics.

Case Material

The following cases are typical for the 15 children under investigation:

Case I

First Admission.—In August 1950, Helen, age 14, and sibling Harry, age 4, were admitted to Children's Center during the night hours. The "mother" had been rushed to the hospital with a cardiac condition and there was no one at home to care for the children. Since Helen spoke very little English, she was interviewed by an interpreter. The girl had arrived from Puerto Rico one month earlier. She had not been aware that her "mother" had been taken to a hospital, but thought that she had deserted after a quarrel with father, who confirmed frequent disagreements with his wife. A subsequent investigation revealed that Mrs. P. is a very disturbed woman who had been diagnosed as "anxiety neurosis" at another hospital. Helen was actually not related to either Mr. or Mrs. P., but had been brought to New York from Puerto Rico by Mrs. P. shortly after Helen's mother had died. When Mrs. P. was well enough to care for the children, both Harry and Helen were discharged to her in January 1951.

Second Admission.—In May 1951 Helen was readmitted to the Children's Center. Mrs. P. refused to keep the girl, claiming she was having difficulties with her husband because of Helen whom she accused of being a trouble maker, of gossiping with neighbors and of telling lies. Helen admitted difficulties with Mrs. P. especially over Harry who often annoyed her and hit her, while Mrs. P. refused to correct him. At times, Mr. P. would come to Helen's defense and that made Mrs. P. angry. Mrs. P. stated she had brought Helen from Puerto Rico because she felt sorry for her. She was the youngest of many siblings; the mother had died of T.B. in June of 1950. A surviving maternal grandmother is very old and unable to care for Helen. The grandmother wanted Helen to go to the United States. A maternal uncle was residing in New York, but he had a large family and could not take care of Helen.

Helen was in good general health during her stay at the Center. Shortly after her second admission she applied to the pediatric clinic because of an ingrown toe nail. She was referred to the Surgical Clinic at Flower-Fifth Avenue Hospital (which is located next door to the shelter), for treatment and was discharged after a few visits. The toe nail became re-infected on two occasions after the original infection had cleared up and Helen returned again to the pediatric clinic. The re-infections were apparently caused by Helen's failure to follow doctor's instructions, namely to cotton pack her nail and to stop putting nail polish on her toes. It was explained to her that irritation of the toe was caused by nail polish. She accepted the explanation but continued to apply polish and failed to cotton pack the toe. Her attitude while visiting the clinic was friendly, cooperative and interested. She urged the nurse at

the pediatric clinic to refer her back to the Surgical Clinic where she had enjoyed the attention of the doctors. She also made frequent visits to the Dental Clinic. While there, she would ask the dentist many questions and would assist the nurse.

Helen complained at the clinic of many minor accidents. The questionnaire shows the following instances: She injured the toe which had been treated previously. She was hit by a ball while sitting on a park bench. She cut herself by using scissors. She fell on the steps and her right ankle became swollen. She was accidentally burned by an electric iron carried by another child. She turned her right ankle and complained about severe pain (X-ray showed no evidence of fracture or dislocation). She complained of a swelling on her head when a boy accidentally bumped into her.

Helen was given a psychological examination in November 1952; on formalized intelligence scales, her rating of "borderline" intellectual capacity might appear to be questionable in view of the patient's poor knowledge of English and her presumed past cultural and formal educational limitations. There is nonetheless rather strong evidence of a "below normal" basic potential in her responses to the projective tests. Certain of her low scores as on Information and possibly, Arithmetic, might be ascribable to an inadequate educational background and her unfamiliarity with facts about her new environment. Her other very low ratings, as on Digit Span and Block Design point to real deficits in memory, concentration, analytic and synthetic reasoning. She shows, in the face of these deficiences, some developed interest and motivation to learn practical, common sense modes of thinking (comprehension sub-test), to focus upon environmental details and to anticipate or prepare for every day social sequences. The quality of her adaptation and thinking processes in these last cited areas—where interest in the outer social scene is tapped—is about "borderline" to "dull-average" in intellectual range.

Her projective tests point to a constricted, shallow range of mental reaction and a very defective capacity to reason and work through important, practical everyday problems. She is vague and phlegmatic in her thinking, rigidly clings to and repeats old modes of response that do not always fit in with simple reality requirements. She is childish, cannot concentrate adequately or remain with a situation for long. Her energy level is low; she frequently blocks or runs away from mild complexities. Aside from showing signs of limited mental functioning, she reveals a personality pattern that inevitably makes for real difficulty in her adjustment. She is anxious, withdrawing in her basic inclination, and yet finds herself pulled to respond to the social situation. Although she makes strong attempts to control herself in her outward adaptation, her ability to discipline her emotions is poor. She is overly-suggestible, frequently misperceives, and misinterprets because of her anxiety and need to appear passive and compliant.

She shows an underlying phobic, hysterical reaction, and tendency to hold in or suppress feelings by straining to be passive and compliant. She has been frightened by her environment and this is reflected in her social and sexual adaptation. There is fear of authority and of males, founded upon her expectation that she will be readily punished or hurt if she is not submissive and compliant. She also shows much fear in expressing her own aggressive inclinations or angry impulses which frequently crop to the surface. Her mode of forced submissive response is in conflict with her phobic regard of the world and her frequent wish to assert her feelings. She constantly holds herself in, adapts to people extra-submissively. This is not surprising in view of her limited intellectual resources, inadequate phantasy outlet, and low frustration tolerance.

She was seen by the psychiatrist, who felt that on the surface Helen has made a good social adjustment. She was poised, made a good appearance in dress, manner and speech. In addition, she is flirtatious and seductive. Psychiatric examination revealed a basically insecure and anxious person. She has an inner awareness of her limitations and might be able to make a satisfactory social adjustment. She presents many hysterical features and retreats into physical complaints when she feels threatened. The tentative diagnostic impression is psychoneurosis, hysterical type in an intellectually limited adolescent.

Follow-up.—Helen became fearful when plans were made to place her in a girls residence. She refused to keep her appointments with the social worker. She showed anxiety and wanted to leave school and go to work. She was at that time attending a Vocational High School, where she was doing well in a dressmaking course. She was discharged from Children's Center in June 1953 because of her age (17 years). A short time after discharge she was reported to have gotten married.

Discussion.—Helen is a rejected child who after the loss of her own family was abandoned by a family which had brought her to New York from Puerto Rico, but left her when her adolescence became a threat to the marital relations of her voluntary foster parents. An immature and anxious child of limited intelligence with submissive, seductive behavior, she tried to satisfy her emotional needs through attachment to the pediatric clinic, where a female pediatrician, also of foreign parentage, represented for her a kind and accepting mother figure. Her behavior at the Center was never disturbing, nevertheless her life adjustment appears poor and her prognosis doubtful. We evaluated the question of apparent accident proneness. We came to the conclusion that she did not have an unusual number of accidents, but tried to use minor incidents as an excuse for frequent clinic visits.

Case II

Admission.—Laura, a Negro, Protestant child born June 1941 was admitted to Children's Center on September 1951 from Bellevue Psychiatric Hospital. She had been referred there from a private shelter when she was acutely disturbed. Deserted by her mother and having been left with neighbors, Laura was placed with the shelter. The mother's whereabouts were not known nor were other relatives located. A neighbor, Mrs. T., was the only known contact who had shown a sustained interest in this child. Anamnestic material reveals marked neglect, frequent abandonment and rejection.

This child's mother was born out of wedlock by a mentally defective woman who was later admitted to a state hospital. This mother had been brought to New York from South Carolina in 1933 by her grandmother. She was slightly less than fifteen when she gave birth to Laura in her grandmother's home. She was then remanded as a delinquent to the Salvation Army Home and Hospital by the Children's Court.

The child's father is not known. At first the child's mother had contended that her maternal uncle, age 30, was the father. Later, she gave the information that she was raped by an unknown man.

Institutional Behavior.—Laura was referred to this Center from Bellevue Psychiatric Hospital for possible placement, but it became evident soon after admission that she was in need of psychotherapy. She showed a behavior pattern of acting out, i.e., running away, frightening and hitting other children, stealing, cursing, indulging in sex play, displaying serious temper tantrums, and threatening to kill herself and others. Consequently she was referred to the Department of Psychiatry.

Clinical Evaluation.—Psychiatric and psychological examinations revealed a child of normal intelligence as shown by performance on formalized test material and interview behavior. Her academic achievements in reading, arithmetic and spelling were commensurate with her grade placement. On the Rorschach she was evasive and unable to cope with this test. Her responses revealed opposition to conventional ideas originating in a strong feeling of insecurity and deepseated anxiety. Rorschach syndromes emerged distinctly as perseveration, oversensitivity, projection of her own aggression upon the environment and hypochondriacal morbidity.

Her TAT and figure drawings were quite revealing. In all of her drawings, there was a morbid element of pathological nature. For example, a child is drawn standing in a garden. The tree has an indentation, "it has been hit by a hatchet", "the door is cracked (open)".

She drew a tree to satisfy a compulsive need to "move the hand in this particular way and keep it from doing wrong". A branch is broken off and leaves are dropping, at the same time she expresses her resentment about "everything sick and drying".

At times her thought processes showed a strong ideational trend with some fluidity. In association, words were used as objects rather than symbols with an occasional use of autistic logic. However, she was able to control the movement away from reality with good intellectual capabilities and showed good recoverability. She showed an ability to identify with people but had structured an erratic concept of her role in life. She can become deeply involved in her social contacts but can not control her affective responses. Thus she gets alternatingly hostile toward and attracted by the same individual and appears therefore unpredictable in her relationships.

Much of her anxiety was related to adolescent sexual problems and to her need for an adult figure with whom to identify. In addition, there was evidence of anxiety about sex, which was seen as highly destructive, and colored by fantasies of aggression and death. In the area of sexual associations she became very upset and morbid. She has not yet identified herself with the female sex. She appears torn between the fear of physical implication and the desire for close personal contact. Ambivalence about danger and safety, aggression and submission dominates her relationships; out-going affection plays a minimal role in her life. A threat of religion was apparent throughout. She seemed to show severe guilt feelings about her own behavior—her running away, her delinquent nightlife, etc. She displayed compulsivity, as an unsuccessful mechanism to relieve anxiety.

During the psychiatric interviews, Laura was pleasant and communicative. She was able to admit her uncontrollable drives and showed considerable anxiety when she talked about her mother's suicidal attempts and frequent quarrels with the boy friend. Miss T. who was Laura's foster mother during the first year of her life symbolized the ideal mother figure. This woman promised her a doll and Laura is still looking forward to the fulfillment of this promise. She also expressed the need for care and attention from Miss T. whom she calls a "decent mother". For Laura, Children's Center was a disturbing environment. She stated, "I would rather be barred up because here I am tempted to run away."

Clinic Visits.—Laura has made a total of 48 visits to the pediatric clinic. Her complaints were always of cold, headache and stomach ache. It was ascertained that she used the clinic constantly in times of stress and when faced with difficult situations.

Diagnostic Impression and Disposition.—Laura has a great deal of anxiety which she can not manage, converting it into acting-out behavior. She actually asks for protection against her own drives. She feels rejected but displays an enormous hunger for acceptance. The diagnosis is that of a behavior disorder with severe anxiety and acting out. It was recommended that she receive psychotherapy. Because her anxiety was so overwhelming and caused a great deal of acting-out, she was treated daily in the early stage of organized therapy.

Follow-up and Discussion: This child received psychotherapy from November 1951 to June 1952; she made excellent progress. However, although she had been prepared for separation, she regressed to her former behavior when her therapist left the institution. During the period in our temporary care, eleven agencies had rejected the child for permanent placement. Having exhausted all possibilities of voluntary placement, court placement was initiated as she could not be adequately controlled in an open shelter during periods of excitement and destructiveness. She was placed in a closed children's home, and later in foster care. There, she made a poor adjustment and ran away three times. The foster mother asked for removal of Laura in 1953 when she was readmitted to our shelter for only one night having run away from the foster home.

Discussion and Conclusion

This paper reports on a selected study of fifteen children in public shelter care representative for a group of frequent visitors to the institutional pediatric clinic. During a period of seven months, all children who visited the clinic were subjected to an intensive study to define the relations of psychological and psychosomatic disturbances to their clinic visits.

The study showed that more than 51 per cent of all clinic visits were caused by 10.5 per cent of the institutional population. An examination of those children who visited the clinic as often as 95 times and not less than 20 times showed an extremely high percentage of psychiatric disturbances. Of the 15 children intensely studied 13 showed psychoneurotic disorders, early neurotic character formation or primary behavior disorder with anxiety (actual) neurosis and 2 were borderline psychotics. We have shown in a previous study the extent of psychiatric disturbances in children in temporary shelter care (1). The group of frequent clinic visitors whom we have investigated in the present paper showed a very high incidence of

psychiatric disturbance as compared with the general population of Children's Center.

Our findings show that the pediatric clinic in Children's Center represents a place of relief, support and protection for the psychiatrically disturbed child who goes there frequently in order to obtain the attention and mothering care of which a large majority of all children in a public shelter have been deprived by their own families. It is obvious that such use of a pediatric clinic does not agree with the primary medical purposes of the pediatric setting. The psychiatrically disturbed frequent clinic visitor represents a heavy burden on the clinic staff, pediatricians and nurses alike. On the other hand, it has to be considered that the psychiatrically disturbed child is in need of additional attention and care which can be given not only by the counselor, the social worker, the psychologist or the psychiatrist but has to be dispensed by all members of the institutional staff. The Pediatric Clinic in Children's Center is part of the psychiatrically oriented residential setting which was described in a previous paper (4).

The understanding treatment of the emotionally disturbed child in the pediatric clinic represents an important part in the training program of the pediatric resident. At Children's Center the attention to the psychological problems of children away from home is an important element in the in-service training program for all staff members including the pediatricians and pediatric nurses.

In order to carry out this integrated approach, one of the psychiatrists attends regularly the pediatric clinic at least once a week in order to acquaint himself with the psychological and psychosomatic problems as they appear in the clinic and at the same time to interpret to the pediatrician the psychological phenomena shown by disturbed children during pediatric attendance.

There are no general rules for a pediatric clinic in the handling of psychiatrically disturbed children. The care has to be highly individualized. As a rule the large majority of these children can profit well from kind and understanding treatment by the pediatrician with or without the use of placebos. In our concept, placebos do not consist solely of internal medication. They might also be applied in the form of dietary prescriptions and physiotherapy.

Frequent clinic visitors should be subjected to psychological and psychiatric examinations so that no serious emotional illness might be overlooked. The screening of children for specialized psychiatric care can best be carried out in the pediatric clinic in collaboration between the pediatrician and the psychiatrist. Close collaboration of these specialities concerned with the health and welfare of children is necessary in order to

lay the basic foundation for the establishment of preventive and therapeutic programs in a childrens institution. The traditional functions of the pediatrician in the physical as well as in the emotional care of children can be enhanced by an understanding psychiatrist (2).

Summary

This paper describes the use psychiatrically disturbed children make of a pediatric clinic in a temporary shelter. The strong inner and outer pressures to which children in sheltercare have been exposed are frequently expressed through physical complaints. The understanding support of medical and nursing care represents a secondary gain for these children, who have been neglected and abandoned by their inadequate parents. The plight of these children has been described in three previous papers by the psychiatric and administrative staff at Children's Center, which is a public, nonsectarian, inter-racial institution where dependent and neglected children between the ages of two and sixteen are sheltered in the City of New York.

Out of a capacity population of 356 children and a yearly turnover of 1780 children, 610 children who visited the pediatric clinic over a period of seven months, between June 1951 and January 1952, have been studied. The present paper is the first publication based on the material obtained through this study. The 5793 visits which were studied through a special questionnaire, filled out by pediatricians and nurses, showed that a small group of children representing only 10 per cent of the resident population, caused more than 51 per cent of all the clinic visits. A special study of the background and the psychological diagnosis of those children who were the most frequent clinic visitors, showed a very high degree of psychiatric disturbance in this small group. Two typical cases of this group are described in detail.

Close cooperation between the pediatric and the psychiatric staffs has been established in order to attend adequately to the needs of the psychiatrically disturbed child, as indicated by visits to the pediatric clinic of the institution. In-service training in the institution is focused on a close cooperation of the staff members with different professional backgrounds (administrator, pediatrician, social worker, psychiatrist, psychologist, counselor, teacher, etc.) whose goal is an integrated institutional program.

Enfants soumis à un stress dans une clinique pédiatrique.

Description d'une étude faite dans une clinique pédiatrique sur des enfants temporairement hospitalisés, lesquels montraient tous un trouble mental. Les fortes pressions internes et externes auxquelles les enfants ont été exposées dans l'asile se sont souvent exprimées par des plaintes physiques. Le soutien médical et celui du personnel infirmier resprésentent une avantage secondaire pour ces enfants qui ont été négligés et abandonnés par des parents incapables. 610 enfants venus à la clinique pédiatrique dans une période de 7 mois ont été examinés. Les 5793 examens faits à l'aide d'un questionnaire spécial complété par des pédiatres et des infirmières ont montré ensuite qu'un petit groupe d'enfants, ne représentant que 10 % de la population résidante, formait plus de 51 % de toutes les visites cliniques. Une étude spéciale de l'arrière-plan et du diagnostic psychologique, faite sur ceux de ces enfants qui venaient le plus fréquemment à la clinique, a révélé un degré fort élevé de trouble mental dans

ce petit groupe. Une étroite coopération entre le pédiatre et le personel psychiatrique a été inaugurée dans le but de subvenir de façon efficace au besoins de l'enfant mentalement troublé.

Unter Spannung stehende Kinder in einer Kinderklinik.

Eine Beschreibung der Benutzung einer Kinderklinik als vorübergehende Unterkunft für psychisch gestörte Kinder. Die starken inneren und äusseren Spannungen, denen Kinder in Schutzfürsorge ausgesetzt sind, offenbaren sich des öfteren in körperlichen Leiden. Die verständnisvolle medizinische Betrenuung seitens des Arztes und des Personals stellt für diese Kinder, die von ihren unfähigen Eltern vernachlässigt und verlassen worden sind, einen sekundären Nutzen dar. 610 Kinder, die in der pädiatrischen Klinik während einer Periode von 7 Monaten aufgenommen waren, wurden beobachtet. Zwecks statistischer Auswertung der 5793 Visiten wurden Fragebogen verwendet, die von den Kinderärzten und Krankenschwestern ausgefüllt wurden. Dabei ergab sich, dass eine kleinere Anzahl Kinder die nur 10 % der dort aufgenommenen darstellte, mehr als 51 % sämtlicher Visiten in der Klinik beanspruchten. Ein eingehendes Studium des Hintergrundes und der psychologischen Diagnose bei den Kindern, die die Klinik am häufigsten besuchten, zeigte, dass unter dieser geringen Anzahl Kinder psychiatrische Störungen in einem sehr hohen Grade festzustellen waren. Eine sehr enge Zusammenarbeit zwischen den pädiatrischen und den psychiatrischen Stäben wurde herbeigeführt, um die Bedürfnisse des psychiatrisch gestörten Kindes vollauf befriedigen zu können.

Tensión infantil en una clínica pediátrica.

Se describe el empleo por parte de niños sufriendo perturbaciones psiquiátricas, de la clínica pediátrica, a título de cobijo temporal. Las grandes tensiones tanto interiores como exteriores a las que los niños bajo albergue están expuestos, se expresan frecuentemente por quejas de orden físico. La comprensión y asistencia del médico y del personal enfermero, representan una ganancia secundaria para estos niños, que han sido descuidados y abandonados por padres incompetentes. Seiscientos diez niños que visitaron la clínica pediátrica durante un período de más de 7 meses, han sido estudiados. Las 5793 visitas estudiadas mediante un cuestionario especial, llenado por pediatras y enfermeras, mostró que un pequeño grupo de niños, representando solo un 10 % de la población residente, ocasionó más del 51 % de todas las visitas clínicas. Un estudio especial de los antecedentes y diagnóstico psicológico de estos niños, los más frecuentes visitantes de la clínica, mostró un grado muy elevado de perturbaciones psiquiátricas en dicho pequeño grupo. Una estrecha cooperación entre el personal pediátrico y psiquiátrico fué establedcida a fin de atender convenientemente a las necesidades de la criatura psíquicamente perturbada.

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The Prophylaxis of Allergic Disease in Infancy and Childhood[1]

by JEROME GLASER, M. D.

The late Dr. Joseph Brenneman (1872–1944), a distinguished pioneer in American pediatrics, was particularly known for his clinical studies of the nutrition of the newborn human infant. About twenty years ago he made the following statement (6): "The milk of every mammal is specific for its young. *To this man is no exception.* (The italics are mine throughout.) There is, furthermore, evidence that the milk of one mammal is not only imperfectly adapted to the young of other mammals, *but that there is even something harmful in non-specific milk.* The essential nature of this specificity is unknown. While it may eventually prove to be largely, or wholly, a matter of chemistry, *there is reason to believe that there is also an intangible biologic factor.*"

It is the thesis of this presentation that Brennemann's statement is correct and that the intangible biologic factor which he foresaw is allergy, and, moreover, that a practical application can be made of this knowledge which will go far towards alleviating the scourge of allergic disease, in the human infant and child.

When I first began practice in 1929, it was the custom of many pediatricians to start infants on raw egg yolk at the age of three months. This method of feeding had been recently introduced because at that time there was very widespread interest in rickets and anemia in infants and egg yolk was believed to be a good prophylactic agent for both. It was soon discovered in the feeding of raw egg yolk to infants three months of age or less that many developed rashes or other evidence of intolerance, and within a few years this practice was almost universally discontinued. Egg yolk subsequently was not introduced into the diet until the age of six to nine months when it was commonly tolerated without difficulty. *This observation suggested that during the interval between three months of age and six to nine months of age, the infant developed some type of protection against allergy to egg.*

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It was well known at that time, as a result of precipitin studies (1, 11) that egg white protein could pass unaltered into the blood stream through the intestinal barrier. Although egg yolk does contain a specific allergen of its own as well as allergens common to egg white, allergic reactions to the specific allergen of egg yolk are extremely rare (8, 32), and reactions to egg yolk, for all practical purposes, are reactions to egg white or to allergens common to egg white contained in the yolk. It was at first thought that perhaps the immunity to egg protein as the infant grew older was due to some anatomic change which would no longer permit the passage of egg white through the intestinal barrier. However, with the development of the passive transfer reaction (30, 33, 35, 36) it was shown that the intestinal tract is permeable to egg white and other proteins at any age. It thus appears evident that the protection against egg white acquired as the infant grows older is immunologic in nature.

On further studying the problem of allergy in early infancy and childhood it became increasingly evident that cow's milk is responsible for many disagreeable allergic phenomena in this age group as has been so ably described by Clein (7). In his practice, which is the practice of the pediatric allergist, the incidence of allergy to cow's milk was estimated at about 7 per cent. The incidence of allergy to cow's milk in early infancy in ordinary pediatric practice is not known, but in the general population of the United States is probably about 1.5 per cent as a minimum (16).

With the knowledge that within the relatively short period of three to six months, infants can develop immunologic protection against such a potent allergen as egg white, the thought occurred that if they could be started on some other food than the traditional cow's milk during this period of physiologic immunologic immaturity, the symptoms of milk allergy might be avoided, minimized or even prevented. That such a possibility existed was indicated by the work of Grulee and Sanford (24) to the effect that seven times as many infants develop eczema on cow's milk as compared with those fed breast milk. It is too often forgotton that breast milk is the only natural food for the human infant, at least during the first few months of life, and that the cow, deserving as she is of the title of "Foster Mother of the Human Race", after thousands of years of domestication, still produces milk primarily designed for calves and not for the human infant (12). It is therefore recommended that in the case of potentially allergic newborn infants breast feeding be urged. For the purpose of this study a potentially allergic infant is defined as one who has one or more allergic parents or siblings.

Since it is well known that almost any food ingested by the mother may appear in the breast milk and cause allergic disturbances in a child sensitive

to that food, the lactating mother is advised to be on a diet low in those foods known to possess high sensitization potential, as egg and cow's milk, and to eat a variety of other foods so as to avoid the risk of sensitizing the infant to any one food which might be eaten in excess. It is also practical, and may even be helpful, to have the mothers of potentially allergic infants on this same diet during pregnancy (17). However, because of lack of ready availability, expense and the difficulty of controlling the diet of wet nurses if the mother does not nurse her infant, breast milk from wet nurses is not practical. The milk of other mammals than the cow is usually not satisfactory because of the close chemical and immunologic relationships of the caseins of the mammalian milks (2). The use of predigested casein preparations has not been very satisfactory in our hands.

Shortly before this work on prophylaxis was started, Hill and Stuart (25) had prepared a commercially available soy bean milk (Sobee, Mead, Johnson & Co.). It was thought that this might be a practical food on which to start a newborn infant from birth as a complementary or supplementary feeding until the infant was six to nine months of age when cow's milk could reasonably be introduced into the diet because the period of immunological immaturity would be past. It was felt that if this was done any sensitivity acquired by the infant would then be to soy bean and not to cow's milk. That this did not happen, however, is explained by the work of Ratner and associates (31). They showed that in contrast to cow's milk, soy bean protein possesses a very low sensitization potential and that the soy bean milk used for the most part in this work (Mull-Soy Liquid—Borden Co.) could not be shown by animal experiments to possess sensitizing properties (personal communication from Dr. Ratner). This is perhaps important in view of the many uses to which the soy bean is now put in the American economy.

A preliminary study was made of the feeding of soy bean to infants from birth. The starting formula was commonly one third normal strength and this was gradually increased to full strength as tolerated with the addition of other foods according to a prearranged design also to assist in the prophylaxis of allergic disease (18). At the age of one year the only difference which could be ascertained between these infants and those fed in the orthodox manner was that more of the experimental infants were over the expected weight for one year than the infants fed by the orthodox methods (20). Parallel to this investigation, which was made in potentially allergic infants, we also carefully watched for the appearance of allergic disease as the child developed.

Our experimental group of potentially allergic infants numbered 96 of which 88 were fed a commercially available soy bean milk (Mull-Soy, Liquid—Borden Co.), 5 meat base formulae and 3 breast milk with the mother on a controlled diet (17). Our first control group consisted of siblings of these infants. It was found that four times as many infants in the control group developed atopic dermatitis (eczema) as

those in the experimental group (21). This is a larger figure than the breast-cow's milk series of Grulee and Sanford (24) and this is attributed to the more careful observation of the infants in private practice than was possible in the out-patient clinics in which they conducted their studies.

When we continued our observations of allergic disease in these children as time went on, it was found, much to our surprise that only about 15 per cent of these infants developed subsequent major allergic disease before the age of six years as compared with the control series. This was of such great importance that another control series was selected consisting of 175 infants unrelated by blood to the infants of our experimental series whose personal and family histories were practically the same as those of the experimental series. In this group 52 per cent developed major allergic disease by the age of six years as compared with about 65 per cent of the first control series. This is truly a remarkably close correlation for this type of biologic work.

It thus appears from the results of these studies that there is approximately a fourfold incidence of allergic disease in potentially allergic children started on cow's milk from birth as compared with those started on a substitute feeding other than cow's milk. The importance of this to the pediatrician, whose main interest is the prophylaxis of disease, is obvious.

The remainder of this discussion will be devoted to a brief consideration of the objections which have been raised to this method of prophylaxis of allergic disease. They are chiefly as follows:

(1) *Soy bean formulae may cause severe gastrointestinal disturbances.*—It was necessary to discontinue soy bean feedings in only 15 percent of all the infants started at birth on soy bean milk because of diarrhea, emesis and sore buttocks. However, all this work was done on one of the older preparations of soy bean milk (Mull-Soy (liquid) Borden—original formula). Since then an improved form of this preparation, as well as other soy bean milks superior to their predecessors, have appeared which have already given better results. A new drug has also been introduced by Blue (5), an extract of Erigeron canadensis, which offers great promise in the treatment of loose bowels caused by soy bean milk.

(2) *Vegetable protein is not as good biologically as animal protein.*—This goes back to the work of Lui and associates (27) in 1931 who stated that so far as hypoproteinemia in relationship to edema is concerned, two grams of vegetable protein are required to produce the same effect as one gram of animal protein. They did not however, take into consideration the soy bean, which is the only member of the vegetable kingdom which possesses all the amino acids necessary for the normal growth and development of the human infant. Block and Bolling (3) reviewed the evidence to the effect that the relative nutritional values of different proteins are based on their content of essential amino acids; i.e., those which cannot be synthe-

sized in the animal body. The source of the amino acids, animal or vegetable, does not matter as long as they are supplied preformed in the diet. That soy bean feeding per se does not result in edema in the eczematous infant has been further discussed elsewhere (15). Other publications attest to the relative equality as regards digestibility of soy bean protein as compared with cow's milk protein (28); its favorable protein efficiency ratio (4); that the amino acid pattern of soy bean is well suited for supplying the needs of the growing animal (10) and crucial experiments with newborn weanling rats indicating the superiority of soy bean protein as compared with cow's milk protein as regards adequacy for supporting growth, reproduction and lactation in multiple generation feedings (26).

The only amino acid in which the soy bean is somewhat deficient is methionine. However, any objection to soy bean protein on this basis is more theoretical than real since this deficiency can be compensated by the additional ingestion of soy bean protein (about 11 per cent the minimal requirements for cow's milk protein (4)) which these infants normally take in the course of satisfying their appetites.

(3) *Soy bean has goitrogenic properties.*—It is well known that some foods have goitrogenic properties, as indicated in the reviews by Greer (23) and by Fertman (9) who stated that it is entirely possible that when the dietary intake is limited almost entirely to these foods the amount of antithyroid substance ingested may be sufficient to prevent thyroxin synthesis and thereby cause thyroid enlargement. Young rats fed exclusively on soy bean will develop large goiters as compared with control rats but this may be completely prevented by giving the rats a normal amount of iodine in their diet. Greer also stated that cooking of the vegetable before eating will probably prevent goitrogenesis. Whatever the facts are as regards experimental animals, in a large experience in feeding soy bean milk to infants as their sole source of protein for many weeks, I have never seen any evidence of goiter in such infants. Both Hill and Stoesser (personal communications), also, have never seen goiter associated with soy bean ingestion. This indicates that either the goitrogenic substance in soy bean is destroyed in the process of preparing the soy bean milk or that there is sufficient iodine in the preparation to neutralize the effect of the goitrogenic substance. If in some areas this should eventually prove not to be true then it would be a simple matter to add sufficient iodine to the soy bean milk to prevent goitrogenesis.

(4) *While it is logical that the feeding of soy bean milk to the newborn will diminish the incidence of allergic disease due to cow's milk during the newborn period and early infancy, it is difficult to understand why this should prevent*

the development of subsequent allergic disease as the child grows older.—The high incidence of subsequent allergic disease developing in children who have had allergic eczema (atopic dermatitis) in infancy and childhood is well documented. Ratner and associates (29) estimated 59 per cent; Vowles and associates (34) 72 percent and the studies in my own practice (19), an incidence of 80 percent. This last figure is higher than the others, probably because the recurrent upper respiratory disorder of allergic origin and perennial allergic rhinitis sufficiently severe to require thorough allergic study are included. It therefore seems reasonable that if atopic dermatitis can be prevented, subsequent allergic respiratory disease may be reduced. A theory which may possibly explain this is as follows:

Just as insulin and related mechanisms are believed to prevent damage to the human organism by faulty carbohydrate metabolism, in the same way we doubtless have a mechanism which protects against damaging (allergic) reactions to proteins and other substances which may at times act as allergens. It seems reasonable to suppose that this latter protective mechanism is in some way related to the activities of the hypothalamus-pituitary-adrenal axis. However, just as proteins are much more complex compounds than carbohydrates, so the mechanism for protection against these compounds is probably very much more complex than the mechanism protecting against faulty carbohydrate metabolism. If we can relieve stress on this mechanism in early infancy by feeding a relatively nonallergic food, such as soy bean milk instead of feeding a food which has a high sensitization potential such as cow's milk, we may be able to avoid straining this mechanism. It might otherwise be so overworked by the early feeding of cow's milk in individuals predisposed by heredity to allergic disease that eczema will develop in the infant who, because of this damaged mechanism, will not be able to resist the development of other allergic diseases as age advances.

Summary and Conclusions

1. A method of feeding the newborn human infant which significantly reduces the incidence of allergic disease, not only during the newborn period but also in later childhood, is reported.

2. The objections to this procedure are considered and it is believed satisfactorily answered.

3. A theory to explain the modus operandi is offered.

4. In a brief communication of this character, many of the facets of this problem cannot be adequately discussed. Most of these are considered in papers not referred to previously in this text (13, 14, 22).

La prophylaxie des maladies allergiques chez les jeunes enfants et dans l'enfance.

Description d'une méthode d'alimentation du nouveau-né, au moyen de lait de graine de soja, laquelle diminue sérieusement les risques de maladie allergique, non seulement pendant le temps qui suit immédiatement la naissance, mais aussi, plus tard, pendant l'enfance. Considération des arguments à objeter contre cette méthode. Présentation d'une théorie expliquent le mode d'action. La brieveté d'une communication de ce genre ne permet pas une discussion convenable des facettes de ce problème.

Die Prophylaxe von allergischer Krankheit bei Säuglingen und Kindern.

Es wird über eine Methode berichtet, mit der neugeborene Säuglinge mit Sojamilch genährt werden. Diese soll das Vorkommen von allergischer Krankheit nicht nur während der Säuglingsperiode, sondern auch nachher, in der Kindheit, bedeutend vermindern. Die gegen dieses Verfahren erhobenen Bedenken werden einer Betrachtung unterzogen. Es wird ferner eine Theorie zur Erklärung des Modus operandi angegeben. Viele Facetten dieses Problems können im Rahmen einer so kurzen Mitteilung wie der vorliegenden nicht genügend erörtert werden.

Profilaxis de la alergia en la lactancia e infancia.

Se informa acerca de un método de alimentación del neonato humano a base de leche de soja, que reduce en forma apreciable la incidencia de la enfermedad alérgica no solo durante el período postnatal sino también durante la infancia. Se enumeran las objeciones en contra de este procedimiento y se considera haberlas contestado satisfactoriamente. Se somete una teoría para explicar el modus operandi. En una breve comunicación de ésta índole, no pueden discutirse, desde luego, como lo merecen, los diversos aspectos del problema.

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Exocrine Gland Dysfunction in Cystic Fibrosis of the Pancreas

by PAUL A. DI SANT'AGNESE

I. Sweat Glands

In 1953 in a series of studies in this clinic (1, 2, 3) it was shown that sweat of patients with cystic fibrosis of the pancreas consistently has a concentration of chloride and sodium two to five times that of normal individuals and of patients (children and adults) with a variety of other conditions. Sweat potassium was also elevated, but to a lesser degree. Chronic lung disease, diabetes mellitus, acquired pancreatic deficiency, cirrhosis of the liver and many other disorders do not per se change the electrolyte concentration of sweat.

Metabolic studies (2) indicated that the abnormally high sweat electrolyte level in patients with fibrocystic disease was not significantly affected by administration of desoxycorticosterone acetate, dietary salt restriction or the occurrence of hot weather. Renal and adrenal function in such patients was found to be normal. It was concluded, therefore, that the defect was in the sweat glands themselves. No explanation has been offered to date as to the physio-pathology responsible for this phenomenon. In the original studies sweat was collected in limited areas of the trunk (1, 2, 3) and presumably came only from eccrine glands. Recently, however, Cooke (4) has found a similar difference in total body sweat between patients with cystic fibrosis and controls.

In Figure 1 (5) are given the figures for sweat chloride values in patients with cystic fibrosis (50–160 mEq/l, mean 106) and for controls (1–60 mEq/l, mean 27). The values for the sweat sodium show a similar difference between patients with fibrocystic disease (70–190 mEq/l, mean 133), and control subjects (10–80 mEq/l, mean 52). The same difference between the two groups was found regardless of whether in patients with fibrocystic disease pancreatic deficiency was present or whether pancreatic function was

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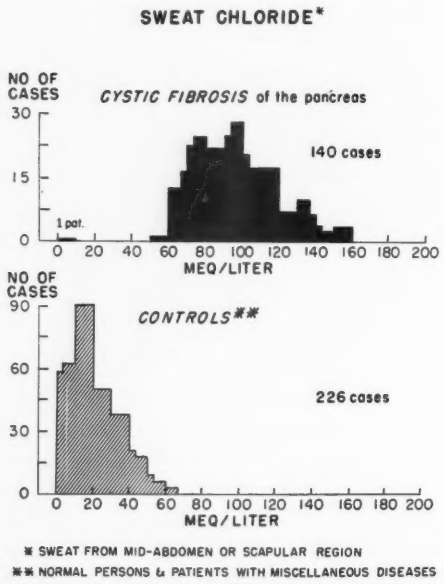

Fig. 1. (From the *American Journal of Medicine* (5)).

preserved. The range for both patients with cystic fibrosis and controls was quite broad, but the overlap between the two groups was minimal.

These findings were subsequently confirmed by Shwachman (6) and others (7, 8). So far we have seen only one patient with cystic fibrosis of the pancreas who had normal sweat electrolytes, out of 140 tested. A similar ratio has been found in other clinics (9).

While this specific abnormality of sweat electrolytes has not been found as yet in any condition other than fibrocystic disease, about 20 per cent of relatives of known patients (parents and siblings) have an increased concentration of chloride and sodium in the sweat (3). Usually these patients have no clinical manifestations of the disease; although at times chronic lung infection is present; however, pancreatic function is normal.

These findings led to important theoretical considerations by showing that cystic fibrosis is in reality a generalized disease in which many and perhaps all exocrine glands, mucus producing and others, are affected. The occurrence of the sweat electrolyte abnormalities in relatives of known patients suggested the existence of incomplete forms of the disease. The knowledge of the markedly increased concentration of salt in sweat and the inability of patients with fibrocystic disease to decrease significantly

these abnormally high levels, gave an explanation of the unusual susceptibility of such patients to hot weather. Massive salt loss through the sweat leads to salt depletion, cardiovascular collapse and at times death (2). From the practical standpoint this knowledge has pointed the way to the prevention and treatment of these complications.

The specificity of the "sweat test" has led to its widespread use in diagnosing fibrocystic disease. It is a valuable diagnostic tool and, furthermore, one which is not dependent on pancreatic function. The introduction by Shwachman (6) of plastic bags to make patients sweat has greatly simplified the procedure as the analysis involved is within reach of most hospital laboratories (1, 2).

II. Salivary Glands

In patients with fibrocystic disease as compared with controls, the concentrations of chloride and sodium tends also to be increased in mixed saliva (10). Potassium is not significantly different. In the experience of our own laboratory, the overlap in values is considerable in the two groups. Prader and Gautier (11), using the average of six determinations in each case tested, found a clear-cut difference in chloride and sodium levels in saliva, between patients with cystic fibrosis and others. The variability in composition of saliva following various stimuli (12) warrants caution in the interpretation of diagnostic data based on electrolyte analysis alone.

We have shown also (10) that the parotid secretory rate is greatly increased in patients with cystic fibrosis as compared with control individuals. This finding is of difficult interpretation; it may be an index of activity of the autonomic nervous system.

III. Mucoproteins of Duodenal Fluid

An abnormality of mucous secretions has been postulated repeatedly (13, 14, 15) in order to explain many of the pathologic findings and clinical symptoms of cystic fibrosis of the pancreas. In recent studies (16, 17), a physico-chemical difference has been demonstrated in the behavior of mucoproteins in duodenal contents of patients with cystic fibrosis of the pancreas as compared with controls.

Material for analysis was obtained by duodenal drainage. Tryptic activity was determined on each specimen. Samples of 1 cc. or more were then centrifuged and the mucoproteins of the supernatant precipitated by adding an ethanol-benzene mixture. In normal individuals and in most patients with a variety of diseases the mucoproteins precipitated in this way are

TABLE 1

The occurrence of a water-insoluble mucoprotein in duodenal contents of patients with cystic fibrosis of the pancreas and controls.

Groups	No. of patients	Age range (years)	Involvement			Water-insoluble mucoprotein
			Pancreas	Lungs	Sweat glands	
Cystic fibrosis of pancreas						
I	49	½–12	+	+	+[a]	+
II	8	½– 7	0	+	+	+
III	1	2	+	+	0[d]	+
IV	6	½– 5	0	+	+	0
Total	64					
Controls						
I	72	½–13	0	0	0[b]	0
II	13	25–73	0	0	not performed	0
III	4	39–66	+[c]	0	not performed	0
IV	3	½–49	0	0	0	+
Total	92					

[a] "Sweat test" performed only in 29 out of 49.
[b] "Sweat test" performed only in 38 out of 72.
[c] Diagnosis in the 4 cases: carcinoma of pancreas in one, chronic pancreatitis in three.
[d] Only patient with cystic fibrosis and normal sweat electrolytes out of 140 tested.

readily soluble in water. In patients with cystic fibrosis of the pancreas a considerable part of the precipitate cannot be redissolved in water, nor brought into solution by the action of trypsin. On analysis the carbohydrate moiety of this water insoluble mucoprotein, did not show significant changes in chemical structure from that of controls.

As seen in Table 1 the water-insoluble mucoprotein was found in 58 out of 64 patients with fibrocystic disease regardless of whether pancreatic function was absent or preserved. The abnormal mucoprotein was absent in 89 of 92 control patients, both children and adults. In the latter group were included normal individuals and a variety of subjects with conditions other than cystic fibrosis. Of the three "control" patients in whom the water-insoluble mucoprotein was found, two were suspected on clinical grounds of having fibrocystic disease. The other in this same group presented an unclassifiable nutritional disorder, with abnormal stools, steatorrhea and malnutrition, but no pulmonary involvement.

In this early stage of the investigation only a few remarks can be made. It is possible that a similar abnormality may be present in the mucous

secretions elsewhere in the body, and studies in this sense are being pursued actively. The absence of the abnormal mucoprotein from duodenal contents of 6 out of 64 patients with cystic fibrosis may find its explanation in the variable involvement of various organs in this disease. By the same token, as either the sweat glands or the pancreas have been found not to be affected in some instances, it is quite possible that some of the "controls" had in reality fibrocystic disease without involvement of both of these areas.

The water-insoluble mucoprotein was present in all of the patients with cystic fibrosis who showed pancreatic achylia, but in only 8 out of 14 of the ones with this disorder who retained partial or normal pancreatic function. Because of the obliteration of pancreatic ducts in patients with achylia of this organ and because of the lack of effect of trypsin on the abnormal mucoprotein, it is not probable that the presence of this fraction is dependent on pancreatic function. However, it may be that patients who do exhibit this abnormality are the ones in whom pancreatic ducts are obstructed by what have been assumed on histological grounds to be abnormal secretions or in whom this sequence of events may eventually take place.

IV. Genetic Considerations

Most of the genetic studies (18, 19, 20, 21) in the past have come to the conclusion that cystic fibrosis is transmitted as a recessive character. Some doubts have been expressed (19) that an uncomplicated recessive trait dependent on a single gene might explain all of the features of the disease.

The situation was altered with demonstration in 1953 (3) that a proportion of relatives of known patients (siblings and parents) had the elevation of sweat electrolytes characteristic of children with cystic fibrosis of the pancreas.

In the past, rigid criteria were assumed for diagnosis of the disease, including absence of exocrine pancreatic enzymes, as well as pulmonary disease or diagnosis at autopsy from the anatomical changes in the pancreas. It is now known (22) that incomplete forms occur in which the pancreas is not affected, though there is chronic lung disease, or even some in which there are no clinical symptoms but the specific electrolyte abnormality of sweat is demonstrated. Our data show that a majority of such individuals are grouped within a relatively few families.

These phenomena suggest that we are dealing with more than one genetic factor. Perhaps the most likely hypothesis at this time, according to Childs (23), is that which calls for a gene or genes which cause the disease in homozygotes and partial expression or no expression in heterozygotes.

V. Summary and Conclusions

It is concluded that, despite the name, cystic fibrosis of the pancreas is a generalized disease in which many and perhaps all exocrine glands are affected (24). Recent studies indicate that there are three different defects in exocrine secretions that need to be explained: (1) A probable abnormality of the mucus secreted giving a reasonable explanation for the pancreatic, hepatic and pulmonary symptoms. This hypothesis has received important support from studies which show the existence of an abnormal mucoprotein in the duodenal content of patients with this disorder. (2) An abnormally high concentration of electrolytes in sweat and in mixed saliva. (3) An increased parotid secretory rate. These several exocrine glands, different in function and in the products they elaborate, are thus affected in different ways.

The basic defect, whatever its nature, appears to be genetically transmitted. A likely hypothesis is that which calls for a gene or genes which produce the fully manifested, though variable, disease in homozygotes and partial or no expression in heterozygotes. In view of some of the findings the possibility that a significant number of the affected heterozygotes exist in the adult population appears to gain some support.

Dysfonction des glandes exocrines dans la fibrose kystique du pancréas.

La fibrose kystique du pancréas est une maladie généralisée dans laquelle plusieurs (et peut-être toutes) glandes exocrines sont atteintes. Des études récentes ont montré qu'il faut expliquer trois différents défauts des sécrétions exocrines: 1) Une anormalité probalbe du mucus sécrété, laquelle donne une explication raisonnable des symptômes pancréatiques, hépatiques, et pulmonaires. Cette hypothèse a été fortement appuyée par des études qui ont révélé l'existence d'une mucoprotéïne anormale dans le contenu duodénal des malades atteints de ces troubles. 2) Une concentration anormalement élevée d'électrolytes dans la sueur et la salive. 3) Une augmentation du taux de la sécrétion parotide. Ces diverses glandes exocrines, différentes dans leur fonction et dans les produits qu'elles élaborent, sont donc atteintes de diverses façons. Quelle que soit sa nature, le défaut basal semble se transmettre génétiquement. Une hypothèse vraisemblable est celle qui parle d'un gène, ou de gènes, produisant la maladie complète, quoique variable, chez les homozygotes et le faisant partiellement, ou pas du tout, chez les hétérozygotes. A la lumière de certaines découvertes, la possibilité de ce qu'un nombre important des hétérozygotes atteints existe dans la population adulte semble gagner du terrain.

Dysfunktion der exokrinen Drüsen bei cystischer Fibrosis des Pancreas.

Cystische Fibrosis der Pancreas ist eine generalisierte Krankheit, bei der viele und möglicherweise sämtliche exokrinen Drüsen betroffen sind. Neue Untersuchungen weisen darauf hin, dass es drei verschiedene Defekte der exokrinen Sekretionen gibt, die erklärt werden müssen: 1) eine wahrscheinliche Abnormität des abgesonderten

Mucus, die als eine akzeptabele Erklärung der pancreatischen, hepatischen und pulmonalen Symptome betrachtet werden kann. Die Untersuchungen, die bei Patienten mit dieser Störung das Vorhandensein eines abnormen Mucoproteins in dem Inhalt des Duodenums nachweisen, haben diese Hypothese wesentlich unterstützt. 2) Eine abnorm hohe Konzentration von Elektrolyten im Schweiss sowie im gemischten Speichel. 3) Eine erhöhte Sekretionsgeschwindigkeit der Parotis. Die verschiedenen exokrinen Drüsen, die sich in ihrer Funktion sowie in den von ihnen erzeugten Produkten unterscheiden, werden also auf verschiedene Weise betroffen. Der Grunddefekt gleich welcher Art, wird anscheinend auf genetischem Wege übertragen. Annehmbar ist die Hypothese, nach der ein oder mehrere Genen in Homozygoten die völlig manifestierte, wenn auch variabele, Krankheit hervorruft, während sich die Krankheit in Heterozygoten nur zum Teil oder gar nicht offenbart. Die Möglichkeit, dass es unter den Erwachsenen eine beträchtliche Anzahl betroffener Heterozygoten anzutreffen sind, scheint angesichts einiger Untersuchungsergebnisse an Wahrscheinlichkeit zu gewinnen.

Disfunción de las glándulas exocrinas en la fibrosis cística del páncreas.

La fibrosis cística pancreática es una enfermedad generalizada en la que numerosas y quizás todas las glándulas exocrinas están afectadas. Estudios recientes indican que existen tres defectos distintos en las secreciones exocrinas, los cuales exigen una explicación: 1. Anomalía probable del muco secretado, como explicaión racional de los síntomas pancreáticos, hepáticos y pulmonarios. Esta hipótesis ha recibido un considerable apoyo a raíz de estudios que demuestran la existencia de una anomalía mucoproteínica en el contenido duodenal de los pacientes afectados por este trastorno. — 2. Concentración anormalmente elevada de electrólitos en el sudor y en la saliva mixta. — 3. Aumento de la proporción secretorio-parótida. Estas diversas glándulas exocrinas, cuyas funciones difieren entre sí, así como los productos que elaboran, quedan pues afectadas de diversos modos. El defecto fundamental, cualquiera que sea su naturaleza, parece transmitirse genéticamente. Una hipótesis plausible consiste en atribuir a un gen o genes, la producción totalmente manifestada, aunque variable, de la enfermedad, en homocigotos y parcialmente o no expresada, en heterocigotos. En vista de algunos de estos descubrimientos, gana cierto terreno el criterio de que hay posibilidad de que exista, en la población adulta, un número apreciable de heterocigotos afectados.

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Primary Tumour of the Heart

Report of a Case

by STAFFAN EDLUND and KAJ HOLMDAHL

During recent years increasing numbers of cases of tumours of the heart have been reported in the literature, and the criteria for establishing the diagnosis in adults have become more exact. However, among children the situation is different. The congenital malformations, with their tremendously varying signs, stand foremost in the clinician's mind, so that tumours localized to any site not producing marked physical signs are more or less predestined to be diagnosed by the pathologist. "Silent" tumours, are nearly always discovered by chance, as in the following case.

Case Report

R. F. (Record No. 228/56), a boy aged 19 months, the only child of healthy parents. Birth-weight 2200 g, forceps delivery. After a short period in an incubator, breast-fed until 2 months of age. Weight-gain and development normal.

There was no cyanosis, but from the age of 3 months the respiration was noticed to be grunting in character, especially when the child was upset. At 15 months, when an operation was planned for the repair of a congenital inguinal hernia, a murmur was discovered, and radiography indicated congenital malformation of the heart. On re-examination at 19 months the child was found to be rather thin, and to have slightly stertorous inspiratory stridor more pronounced in the prone position. He then weighed 10.3 kg and was 81 cm tall. Apart from the circumference of the head (51.5 cm), some prominence of the frontal bones, and the cardiac signs, nothing abnormal was found. The haemoglobin concentration was 12.0 g/100 ml and the erythrocyte count 4.1 million. There was no cyanosis or finger-clubbing.

Examination of the heart.—There was a slight prominence on the left side of the chest. No thrill could be felt. A soft (grade 2–3) systolic murmur was heard over the whole precordium, maximum over the third and fourth intercostal spaces, and not conducted radiating. There was no diastolic murmur. A_2 and P_2 were normal. The femoral pulses were clearly palpable. The blood pressure was 80/40. On screening the heart was found to be generally enlarged, with lateral bulging of the ventricles. No hilar pulsation or more than average pulmonary vascularity were noted. Electrocardiography revealed signs of impairment of ventricular conductivity and a suggestion of myocardial anoxia, but no clear signs of hypertrophy (Fig. 1).

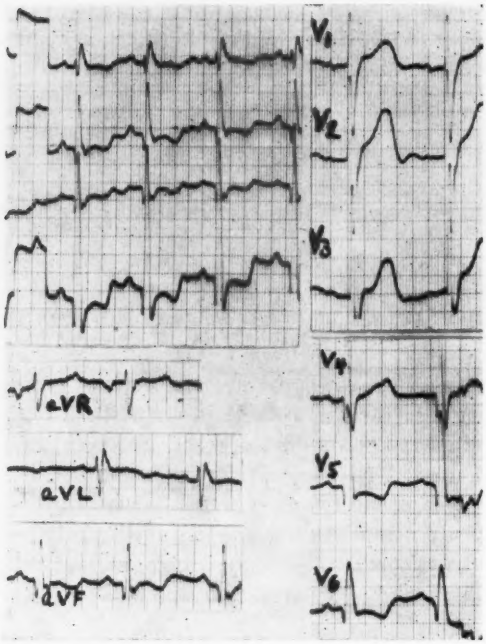

Fig. 1. EEG: Signs of impaired ventricular conduction.

Radiogram (Fig. 2).—Cardiac volume 210 ml, corresponding to 435 ml/sq.m. body surface (normal limits 295 ± 30.4 ml, according to Eek 1949). Lateral enlargement of the heart in both directions, elevation of the apex.

Cardiac catheterization (via the left cubital vein).—Nothing abnormal in the superior vena cava or right atrium, but impossible to penetrate farther.

Biplane angiocardiography (Fig. 3).—The catheter is lying in the superior vena cava. The right atrium is normal. The right ventricle, which is of normal size, is displaced to the right and is lying in front of the right atrium. It has a concave left border. The pulmonary vessels are normal. The left atrium is enlarged. The left ventricle is normal in size, but is greatly displaced to the left by a mass at the apex which renders protuberant the left border of the filled ventricle. The mass consists of a smooth, ovoid tumour measuring 5.5. cm in diameter and showing no vessels. No contrast medium has entered the tumour.

In addition angiocardiography revealed persistent ductus arteriosus (small, to judge from the opacity of the vessel) and, at the same level, slight coarctation of the aorta.

The tumour showed no signs of malignancy, and at the wish of the parents operation was postponed for a year. In the meantime the patient thrived and was in good health, but dyspnea was noticed when the child was playing actively.

On re-examination at 32 months the stridor was found to have disappeared. The child now weighed 12.8 kg and was 93 cm tall, with a head-circumference of 53 cm.

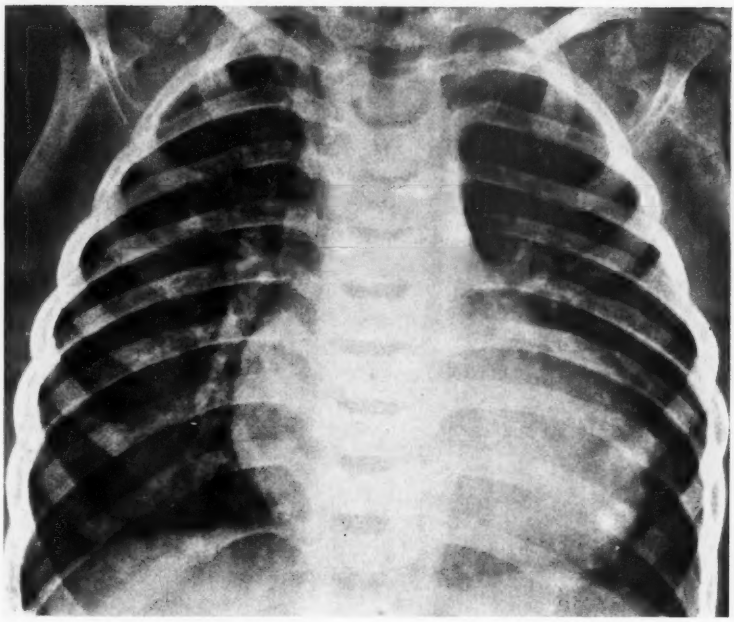

Fig. 2. Frontal view showing the left-sided enlargement.

A systolic murmur (grade 1, i.e. weaker than formerly) was heard at the base of the heart, and the other physical signs were unchanged. The blood pressure was 95/60 in the arm and 110/70 in the leg. The electro-cardiographic changes were more pronounced, but there were no clear signs of hypertrophy. *Screening* revealed slight pulsations at the apex, but otherwise the findings were the same as before.

Radiogram.—Cardiac volume 335 ml, corresponding to 420 ml/sq.m. body-surface (normal limits 304 $\pm$ 41.5 ml). The cardiac configuration was as before.

Thoracotomy was performed by Paul Rudström, M.D., in order to close the ductus and inspect the tumour. On opening the greatly distended pericardial sac the ventral surface of the left ventricle was found to be occupied by a poorly defined mottled tumour with an uneven surface (see Fig. 4), extending to the coronary sinus and displacing the anterior branch of the coronary artery. The gross appearance suggested a dermoid. It seemed too hazardous even to take a specimen for biopsy. The ductus was found to be very narrow, and was therefore not closed. The postoperative course was uneventful.

Dermoid tumours of the ventricle are extremely rare, to judge from reports in the literature. The appearance of the lesion and the clinical findings tally fairly with descriptions of fibroma of the heart (see McCue *et al.*, James *et al.*).

Tumours of the heart, no matter what their type, usually lead to death from impairment of cardiac function.

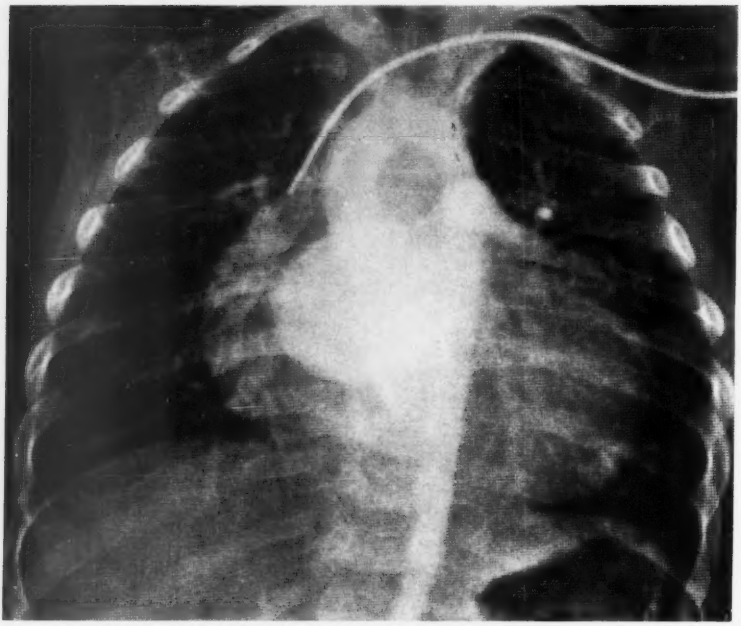

Fig. 3. Frontal angiocardiogram showing the left atrium and the left ventricle displaced by the mass in the left side of the heart. The aorta is filled, and also the pulmonary artery owing to the persistent ductus arteriosus.

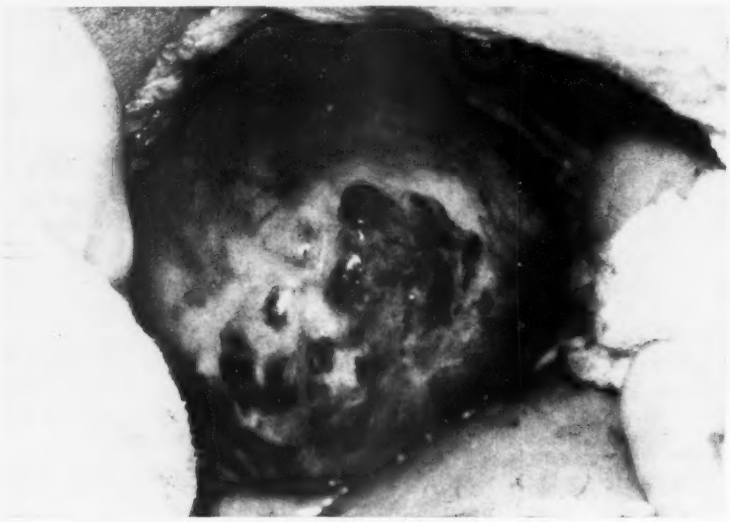

Fig. 4. Appearance of the apex.

Summary

A case is reported of tumour of the heart in a boy of 19 months. The lesion was situated in the left side of the heart, and on thoracotomy at 32 months was found to be inoperable. Biopsy was not undertaken, but the diagnosis of fibroma (dermoid) is put forward, in view of other reports in the literature.

Tumeur primaire du cœur. Rapport d'un cas.

On décrit le cas d'une tumeur du cœur chez un garçon âgé de 19 mois. La lésion se situait au côté gauche du cœur et s'est révélée être inopérable lors de la thoracotomie à l'âge de 32 mois. On n'a pas pris de biopsie, mais, vu les autres rapports dans la littérature, on posa le diagnostic de fibrome (dermoide).

Primärer Herztumor. Beschreibung eines Falles.

Es wird der Fall eines Herztumors bei einem 19 Monate alten Knaben beschrieben. Der Prozess befand sich an der linken Herzseite und wurde bei einer Thorakothomie im Alter von 32 Monaten als inoperabel erkannt. Eine Biopsie wurde nicht durchgeführt, aber auf Grund anderer Literaturberichte wurde die Diagnose Fibrom (Dermoid) gestellt.

Tumor primario cardíaco. Descripción de un caso.

Se describe el caso de un tumor cardíaco en un joven de 19 meses. La lesión estaba situada en el lado izquerdo del corazón y al practicarse la toracotomía a la edad de 32 meses, se comprobó que era inoperable. No se hizo biopsia, pero, en vista de otros casos en la literatura, el diagnóstico fué fibroma (dermoide).

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Visceral Larva Migrans

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In 1952, several members of our group proposed the present title as an appropriate one for a peculiar and rather characteristic "meandering" type of visceral parasitism—analagous to creeping eruption in many respects (1). Though this disease might be expected to occur in a variety of circumstances, the most familiar setting—expected earlier and now confirmed by a larger experience—is the toddler or preschool child who eats dirt containing infective larvae of *Toxocara canis*, indiscriminately deposited about the door yard by a pet puppy (2, 3).

Though creeping eruption (cutaneous larva migrans) had long since been described and the term generally accepted, and though visceral parasitism was known in animals (4), earlier reports dealing apparently with this same condition in humans had been interpreted and had appeared under a variety of titles. It seems now, however, that the name has "caught on", as judged by a number of publications, communications, and conversations during these several years (5–13). We have studied 28 reasonably typical cases in our own hospital, and have knowledge of one or several individuals from at least ten states and a number of reports or specimens from other areas.

Among young children, most cases have been characterized by conspicuous hepatomegaly, eosinophilia, and hyperglobulinemia quite literally "picked up" incident to studies for apparently unrelated disease which first brought the patients to medical attention. A considerable number are first suspected by careful inquiry into opportunities for ingesting foreign nematode larvae when parents consult physicians in concern over such protean symptomatology as low-grade fever, irritability, loss of appetite, poor weight gain, changes in behavior, and anemia—"not quite up to par". A third, and so far smallest, group are recognized during household and neighborhood surveys among apparently healthy siblings and playmates of proved cases.

[1] Presented at the VIII International Congress of Paediatrics, Copenhagen, 27 July 1956.

At present, our patients are about equally divided as to evidence of associated parasitic diseases; in about half the sample, appropriate repeated examination discloses no ova, cysts, or parasites in the feces, while in the other half one or more such are present—particularly *Ascaris lumbricoides*. As might be expected, the degree of polyparasitism appears related to reasonably obvious environmental and socio-economic considerations, though the sample is not yet adequate to establish this point with statistical certainty. By the same token, associated nonparasitic disease or deficiency states would also be expected to be more frequently encountered in the least favored groups.

Among patients lacking satisfactory evidence of coincident ailment which might be confusing, often bizarre manifestations may be related to the more or less adventitious localization of larvae and their consequent granulomatous reactions (14). Among our young patients, as well as in experimental animals, we have reason to believe that lesions may commonly occur in any organ or all organs, except perhaps the spleen (15). Though splenomegaly of mild or moderate degree among young children with febrile disease is so commonly encountered as to have little positive differential significance, we have not yet encountered any specific lesions in the spleens of experimental animals at any time following known infection with *Toxocara canis*. Furthermore, though cutaneous and subcutaneous lesions are not unusual in mice fed foreign larvae, we have so far failed to demonstrate the organisms in biopsies from a variety of superficial nondescript granulomatous lesions encountered in children who had visceral larva migrans proved otherwise.

Though there is no practical way to measure the size of the infective dose of larvae under natural conditions, it appears reasonable to speculate that the severity and localization of symptomatology might be related to the number of these ingested; under natural conditions a child might be frequently infected with very few or several thousand larvae at a time. Such a quantitative relationship would appear logically to explain a spectrum of symptoms ranging from a child who appears and acts entirely well with only a conspicuous eosinophilia, to one whose general appearance justified a preliminary working diagnosis of leukemia or one of the collagen diseases (6). Thus, in two patients who received small doses of 200 embryonated eggs of *Toxocara canis*, promptly followed by conspicuous eosinophilia which persisted for at least 13 months, other symptoms or signs of the disease such as fever or hepatomegaly, were most trivial or transient (15).

Though final proof of diagnosis still depends on demonstration of typical lesions and identification of specific larvae in biopsy specimens, usually from the liver, we no longer carry out or advise this procedure routinely in

practice. When the epidemiologic and clinical features, previously described, are present in a child with chronic eosinophilia and hyperglobulinemia, we are content to break contacts, to watch, to wait, to support, to take steps to prevent other infections, and to depend on a generally benign course; exceptions should soon be evident in the individual child which would justify other plans.

Experimental Work

Since identifying larvae of *Toxocara canis* as a cause of human disease, important advances have been made in our knowledge as to morphology, development, and migratory behavior of this and other species of nematode larvae. Earlier, it was known only that *T. canis* in its normal dog host followed the same life cycle pattern as did *Ascaris lumbricoides*, developing to an infective stage within its shell in contaminated soil, then being swallowed, hatching in the small intestine, thence making its migration up through the liver and lungs and back to the intestine. It was known also that prenatal infection occurred commonly, larvae of either *Tococara canis* or *Ancylostoma caninum* in bitches presumably crossing placental barriers at a strategically critical time in their migration during gestation, adult worms then reaching sexual maturity in puppies three or four weeks old (16, 17).

Sprent (18) observed two distinct patterns of migration when diverse species of ascarid larvae were introduced into laboratory mice. Those of *Ascaris lumbricoides* behaved in much the same manner as in their usual human host, growing rapidly as they passed from intestine to liver to lungs–then returning directly to the intestine. But failing for any reason to find their way through the trachea to the alimentary tract they perished in the tissues within about three weeks. *Toxocara* and some other species of ascarid larvae, on the other hand, did not follow such a tracheal route in mice, but rather remained in or re-entered the blood stream from the lungs and were disseminated to brain, kidneys, muscles and other parts—where they persisted for long periods. Sprent designated this type of behavior "somatic migration", and Baer (19) proposed the term "paratenic" for hosts biologically unnecessary ("prolonged") and in which larvae do not attain maturity. Working with ascarids of skunks and raccoons, Tiner (20) had also noted this peculiar somatic type of migration in mice and had suggested it as a normal intermediate host-relationship between the ascarid, the mouse, and the predator type of final host. This idea was further developed by Sprent (18) who recently reviewed the whole subject of ascarid life cycles. Other studies have shown that *Toxocara canis* larvae behave similarly in mice, rats, hamsters, guinea pigs, rabbits, nutria, monkeys, pigeons, and young chickens. Apparently without growth and without losing their infectivity

for other animals, they may persist in many tissues for as long as two or more years (21).

While larvae of *T. canis* are widely distributed in tissues of animals, they tend to accumulate in some organs more than in others and to differ both in location and in persistence among the different hosts. However, judging from findings in many experimental animals, in necropsy of one (14), and biopsy of several humans, the organs most commonly invaded in children are probably the liver, lungs, and central nervous system—in this order. No major organ adequately studied has been found consistently free from larvae except that they are notably uncommon in the spleen. So far, bone has not been adequately studied.

Early in the infection larvae move very actively within individual organs, and from organ to organ. After a few weeks or months, depending upon factors not yet understood, the larvae become less mobile, and more or less encapsulated. However, such encapsulation does not in itself destroy the larve; there is even evidence that larvae at times voluntarily abandon capsules and resume migration (4). Ultimately they disappear from the body, but it is not yet known whether all of them perish in tissues or are, in part, eliminated through fortuitous tracheal migration.

Pathology

Three general types of pathology have been observed in infected children. Early, due to active migration, linear granulomata are formed, resulting in tissue damage that is relatively extensive in relation to number of larvae involved. Later, predominant lesions are fibromatous capsules immediately surrounding these larvae. The third, and apparently most damaging type, results from a generalized hyperergic reaction (6).

Linear granulomatoses, seen in early phases, are reminiscent of those characteristic with cutaneous larva migrans, in which the inflammatory reaction progresses and regresses in the wake of the moving larvae, while in the immediate vicinity of the organism there may be little or no microscopic evidence of tissue injury. Initially, a few neutrophiles and lymphocytes accumulate in the trail, but soon the massive infiltration is conspicuously eosinophilic. Later on, or further from larvae, a few epithelioid and giant cells may be seen and the lesion expands to involve a relatively wide area, in which normal tissue architecture is lost. Whereas the larva is only about twenty microns in diameter, the linear lesion produced in its wake may be two or three hundred times wider. Reactions are generally more pronounced in the immediate vicinity of blood vessels, and extensive perivascular infiltration may occur some distance from the primary lesion. Charcot-Leyden

crystals are infrequently encountered in "paths" made by moving larvae. Regression and then regeneration follows the usual course of healing.

The focal lesions which soon develop around relatively immobile larvae differ from these linear ones. Massive eosinophilic infiltration is followed by epithelioid and giant cells which in turn are replaced by fibrous tissue to form eventually firm, regular capsules. This encapsulation apparently is slowest in the brain. As lesions become more organized, Charcot–Leyden crystals are formed, sometimes abundantly, both within and outside these fibrous margins.

Hyperergic reactions to *Toxocara* larvae have been described by Brill, Churg, and Beaver—consisting chiefly of extensive degeneration and a variable amount of inflammation in striated muscles, particularly in the diaphragm.

Identification of Nematode Larvae

Rarely, a nematode larva may be found in sputum, and its identification can be readily made by fairly complete morphologic criteria. Free larvae are more likely to be recovered in tissues obtained from biopsy or necropsy; these can often be teased or digested out for complete study (22). Usually, however, larvae are observed in tissue sections, which contain small portions of the organism cut at various angles and levels. Numerous serial sections may permit a more or less complete reconstruction, but in any case identification of such larvae in sections requires careful study by an experienced worker. Until recently, it was not possible to differentiate between larvae of even groups as unrelated as ascarids and hookworms. Moreover, even tissue-invading stages of the nematode parasites that usually occur in man had not been described in detail. Immediately following identification of larval *Toxocara canis* in a liver biopsy (1), incidentally based on rather meager knowledge of its morphology then available, Nichols (23, 24) carried out studies which have made it possible to identify quite accurately in tissue sections the larvae of *Ascaris lumbricoides*, *Necator americanus*, *Strongyloides stercoralis* commonly expected in humans, and those of *Toxocara canis*, *T. cati*, and *Ancylostoma caninum* which normally occur in dogs and cats but also invade human tissues, as the probable chief offenders in producing visceral larva migrans. In some parts of the world, other species may be of greater importance, and in all areas we must assume that any number of species found in other animals may occasionally be encountered as the causative organism for this disease in man.

Toxocara canis, which has been most frequently established as a cause of visceral larva migrans, invades human tissue as a second-stage larva. Fortunately, from the standpoint of diagnosis or identification, its morphol-

ogy and size as seen in the egg recovered from soils or cultures is essentially unchanged after it reaches and remains for long periods in tissues of human or other hosts. Based on Nichols' observations, *T. canis* larvae may be recognized by the following characteristics: length, about 400 μ, greatest width, 20 μ; mouth slightly subterminal under a prominent prow-like ventral lip; esophagus 150 μ long with a bulb-like expansion at its junction with the intestine; intestine poorly developed, represented by a chord of seven cells compressed between right and left excretory trunks which extend from slightly anterior to the esophageal bulb posteriorly two-thirds the length of the intestine; anus 40 μ from tip of tail; tail somewhat abruptly tapered from level of anus, and usually flexed dorsal. The most conspicuous features seen in transverse sections through levels of the mid- or fore-intestine are the paired, round, lateral, excretory trunks within the thin body wall, and the lateral alae which are vertical thickenings of the outer cuticle appearing as sharp spine-like structures in transverse sections (23).

Serodiagnosis

Jung (25) and Heiner (12) have made encouraging progress towards developing serological aids in the diagnosis of visceral larva migrans but their work is still highly experimental. Jung is testing an antigen prepared from infective-stage *Toxocara* larvae, comparing it with one similarly prepared from larvae of *Ascaris lumbricoides*; thus far he has found strong cross reactions when these are used either for intradermal or precipitin tests. Heiner's antigens are prepared from adult worms and apparently give a more specific precipitation reaction in gel, but lack specificity when used intradermally.

Problems in Differential Diagnosis

Actually, we feel that there are few, if any, chances for confusion when the physician is confronted by a pale toddler who has eaten dirt contaminated by a pet puppy, who has conspicuous hepatomegaly, eosinophilia, and hyperglobulinemia, and whose parents complain that the child has such symptoms as unusual irritability, lassitude, anorexia, and irregular low-grade fever.

In our experience, conditions most apt to be of concern in the early phases of the disease are eosinophilic leukemia, the pulmonary stage of ascariasis, infection with *Capillaria hepatica*, and perhaps very temporarily a number of common allergic diseases and a few rare cases of polyarteritis and other members of the "collagen family". While biopsy proof remains as the best diagnostic procedure when any of these seem to justify serious

concern, a little time usually suffices to solve the diagnostic problem in the individual patient.

Eosinophilic leukemia, if it occurs at all in children, is certainly extremely rare; we have never encountered a case. Proper and periodic hematologic studies should suffice to distinguish the exceptional acute leukemia in which eosinophilia may be transiently prominent.

At a first or single examination, infection with *Ascaris lumbricoides* is most apt to cause confusion. As noted previously, and as can be logically expected by environmental circumstances, polyparasitism is present in many cases of proved visceral larva migrans due to *Toxocara canis*. Passage of adult ascarids, presence of ova in the feces, estimation of worm-load, conspicuous pulmonary symptoms and signs, and response to antihelmintic and antibiotic therapy usually suffices to satisfy us that we are dealing with active early ascariasis. Furthermore, eosinophilia accompanying infection with *Ascaris lumbricoides* is transient and certainly does not persist at high levels for more than three weeks or so after effective conventional therapy, unless there has been prompt reinfection. This problem is then resolved, realizing that infection with *Toxocara canis* and *Ascaris lumbricoides* may coexist, and that the eosinophilia due to *Ascaris lumbricoides* alone tends to subside early in the course of this infection despite the presence of immature or mature worms in the intestine (26). Nothing other than prevention of reinfection and general supportive care so far appears to modify the chronic course of visceral larva migrans as we have encountered it. Contrariwise, when we are dealing with massive ascariasis, the issue will have been settled within a few weeks quite definitely and clearly in practically all instances.

Infection with *Capillaria hepatica*, so far as we can determine from a recent report (27), may produce the evidences we have come to consider quite diagnostic of visceral larva migrans; because it is still impossible to differentiate on clinical grounds after one or several appraisals over a period of more than several weeks, it constitutes an indication for biopsy as the *only* means for differentiation.

Because there is a body of evidence favoring the notion that several infections in chronic or recurrent forms may produce symptomatology fitting one or the other of the "collagen" diseases which might occasionally present with symptoms suggesting visceral larva migrans, here again we have diagnostic and prognostic justifications for biopsy-in-doubt (28).

We fully expect that infection with nematode larvae of various sorts may cause similar if not identical clinical features. Speculation and recorded experimental observations, reviewed here and elsewhere, strongly caution against a conclusion that *Toxocara canis* is *the* single or even major causative

agent for visceral larva migrans. If our theories are correct, any of a large variety of nematodes *may* be involved, depending of course largely on peculiarly local epidemiologic considerations.

To dispose of a large number of common extrinsic or intrinsic allergic disorders, suffice it to say that in our experience these so far have caused no serious confusion whatsoever.

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Summary

A peculiar meandering type of visceral parasitism has been described, affecting particularly young children, and due to ingestion of infective nematode larvae—usually *Toxocara canis*—the common roundworm of dogs. This condition appears to occur fairly frequently, and to be widely distributed.

Prior to 1952, when larvae were first specifically identified in tissues, the disease had been reported under a variety of titles, emphasizing in common a conspicuous eosinophilia; a number of other features have since been added.

Experimental work has served to elucidate fairly clearly the probable mechanisms involved in the natural course of the disease. Research efforts are proceeding in three main directions: First, development of indirect diagnostic procedures for establishing the presence of various specific nematode larvae, in order to bypass the necessity of biopsy for their precise identification. Second, emphasis on prophylaxis and specific curative therapeutic procedures. Third, studies to explore the roles of various other parasitic agents, with a view to discovering the frequency of this pattern of disease they might cause in humans.

Finally, it is hoped that this review will, by provoking interest in this intriguing complex, lead to further studies elucidating the many variations expected in symptomatology, and then to an early solution of the therapeutic challenge it poses.

Larve migratrice de l'intestin.

On décrit un type particulier et variable de parasitisme atteignant spécialement les jeunes enfants et provoqué par l'ingestion de larves infestants de nématodes — d'habitude de *Toxocara canis* — le ver rond habituel du chien. Il semble que cette affection se produise assez fréquemment et soit largement répandue. La maladie avait déjà été décrite avant 1952, lorsque les larves furent pour la première fois spécifiquement identifiées dans les tissus, sous une variété de titres qui mettaient tous l'accent sur une remarquable éosinophilie. On y a ajouté depuis lors un certain nombre d'autres propriétés. Des travaux expérimentaux ont aidé à élucider bien clairement les mécanismes probables qui interviennent pendant le processus naturel de la maladie. Les recherches se poursuivent dans trois directions principales. Premièrement : développer des

procédés de diagnostic indirect pour établir la présence de larves spécifiques différentes de nématodes dans le but d'éviter la nécessité de faire une biopsie pour leur identification précise. Deuxièmement : insister sur la prophylaxie et les procédés de traitement spécifique. Troisièmement : explorer le role que jouent des parasites autres et différents, afin de découvrir la fréquence de ce genre de maladie, qu'ils peuvent causer chez l'homme. On espère enfin que cette étude conduira, en suscitant de l'intérêt pour ce complexe curieux, à des recherches ultérieures qui expliqueront la grande variété des symptômes et ensuite une solution rapide du problème thérapeutique qu'il pose.

Wanderlarve des Darmes.

Es wird ein besonderer und variabler Typ von Parasitismus beschrieben, der besonders junge Kinder befällt und durch Verschlucken von Nematodenlarven des gewöhnlichen runden Hundewurmes — *Toxocara canis* — verursacht wird. Es scheint als ob diese Affektion ziemlich häufig vorkommt und weit verbreitet ist. Die Krankheit wurde schon vor dem Jahre 1952 beschrieben. Damals konnten die Larven zum erstenmal spezifisch durch verschiedene Kriterien im Gewebe nachgewiesen werden. Vor allem fand man eine hochgradige Eosinophilie. Seitdem ist es gelungen, eine Anzahl weiterer Eigenschaften herauszufinden. Die experimentellen Arbeiten haben dazu beigetragen, den wahrscheinlichen Krankheitsmechanismus aufzuklären. Die Forschungen folgen dabei drei Hauptrichtungen: Erstens: Man entwickelt indirekte diagnostische Metoden zum spezifischen Nachweis der sich von den Nematoden unterscheidenden Larven, um dadurch eine Biopsie zum Zwecke ihrer genauen Identifizierung vermeiden zu können. Zweitens: man befasst sich genau mit Problemen der Prophylaxe und der spezifischen Behandlungsmethoden. Drittens: Man erforscht die Rolle, die andersartige Parasiten spielen, um dadurch etwas über die Häufigkeit erfahren zu können, mit der diese Krankheit beim Menschen vorkommt. Man hofft, dass diese Studien dazu führen werden, das Interesse für diesen eigenartigen Komplex wachzurufen, damit ein weiteres Studium der grossen Vielfältigkeit dieser Symptome eine schnelle Lösung der therapeutischen Probleme ergibt.

Larva migratoria del intestino.

Una clase especial de parasitismo de la viscera ha sido descrita. Esta forma afecta principalmente a niños y es causada por ingerir larvae de nemtaodos, principalmente *Toxocara canis*, en estado infeccioso. Parece que esta condición ocurre con frecuencia y que es de distribución amplia. Antes de 1952, fecha en que las larvae fueron especificamente identificadas en tejidos humanos, la enfermedad era conocida bajo varios nombres teniendo como factor común una eosinofilia marcada. Desde entonces muchos otros detalles han sido añadidos. Trabajos experimentales han aclarado los mecanismos probables del curso de la infección. Corrientemente las investigaciones siquen tres rumbos principales, primeramente el desarrollo de un metodo diagnostico indirecto para poder percibir la presencia de varias especies de larvas sin tener que recurrir a biopsias. En segundo lugar énfasis sobre profilaxis y metodos terapéuticos. Tercero, estudios de otros parasitos para determinar con que frecuencia producen síntomas parecidos o iguales en seres humanos. Por ultimo es de desear que esta revisión provocará interes en este sindrome complejo y lleve a otros estudios para determinar las multiples variaciones en la sintomatologia y una solución rapida del problema terapéutico.

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Glycogen Content in the Placenta of Diabetic Mothers

by FRANK HEIJKENSKJÖLD and CARL A. GEMZELL

In 1859 Claude Bernard demonstrated glycogen in the placentae of rabbits. Later, numerous investigations on glycogen content in the placenta of man and animals have been published and have confirmed the findings of Bernard (Gordon & Villee, 1954; Huggett, 1929 and 1954; Lochhead & Cramer, 1908; Villee, 1953a, b).

It has been shown that the human placenta has a maximum glycogen content at the eighth week of pregnancy, followed by a successive decrease until full term. The glycogen is localized in the maternal part of the placenta (Dempsey & Wislocki, 1944; Maximow, 1898; Tuchmann-Duplessis & Bortolami, 1954) and is rather stable against factors that will cause a depletion of glucose in the maternal blood or a depletion of glycogen in the maternal liver (Huggett, 1929).

In early pregnancy the foetal liver lacks glucose-6-phosphatase which is necessary for the production of glucose from glycogen (Villee, 1953b). In the ninth week of gestation the liver of the human foetus begins to accumulate glycogen and the content increases thereafter. The glucose-6-phosphatase enzyme, however, is not developed until after the twelfth or the fifteenth week of gestation. As the foetal liver is unable to produce glucose from glycogen in early pregnancy, it is thought that the placenta acts as a carbohydrate depot for the foetus.

Extensive studies in vitro on placental metabolism have been done by Villee (1953b). He reported that placentae from early gestation had a marked ability to synthesize glycogen while full term placentae had almost lost this ability. Hydatidiform mole or placentae from mothers with toxaemia showed the same ability to synthesize glycogen as placentae from mothers with a normal pregnancy. Administration of hormones to the incubate medium showed an increased glycogen formation for insulin while cortisone decreased the formation of glycogen.

This paper is concerned with the content of glycogen in placentae of diabetic mothers.

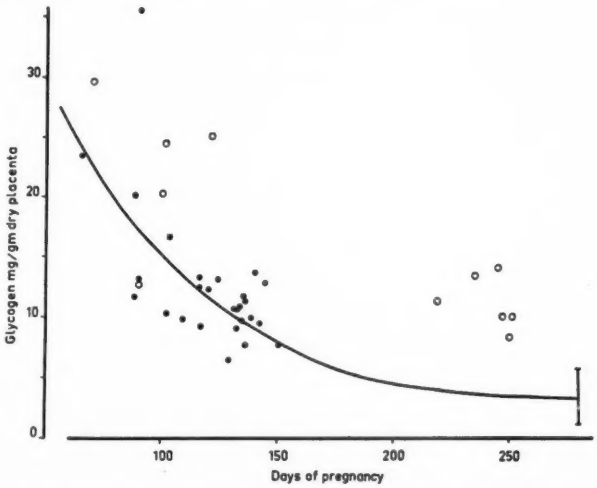

Fig. 1. Correlation between the concentration of glycogen in the placenta and the duration of pregnancy (in days). ○, diabetic mother; ●, non-diabetic mother.

Material and Methods

Placentae were collected from therapeutic interruptions in early pregnancy, from normal deliveries at full term and from Caesarean sections, usually three weeks before full term. They were immediately frozen with solid carbon dioxide in a thermos bottle. Membranes, umbilical cord and blood clots were removed. After weighing, the placentae were stored at —20°C until further treatment. The placentae were then ground to a homogeneous mass. Thawing was prevented by the addition of solid carbon dioxide. The homogeneous mass obtained from each placenta was lyophilized. After precipitation and purification the glycogen was estimated according to the method of Seifter, Dayton, Novic & Muntwyler (1950).

Insulin was administered to all the diabetic patients in this study (Table 1). The daily dose of insulin varied between 32 and 92 IU. The urinary output of glucose varied between 0.5 and 5.0 per cent. No patient had acetone bodies in the urine. The newborn infants of the diabetic mothers had no signs of illness though some of them were rather oedematous in the initial post-natal period (Table 1).

Twenty-five early and sixteen full term placentae from non-diabetic mothers and five early and six full term placentae from diabetic mothers were investigated. Five of the six full term placentae from the diabetic mothers were obtained at Caesarean section, usually in the 37th week of gestation.

Results

In Fig. 1 the glycogen content of the placentae is plotted against the length of pregnancy in days, calculated from the first day of the last menstrual period. In early pregnancy the placental glycogen content was found to be high, thereafter it decreased successively until the time of parturition.

TABLE 1

Case histories.

No.	Pat.	Age (years)	Obstetric	Duration of diabetes (years)	Daily dose of insulin (I.U.)	Remarks
1	G. I.	19	0-para Therapeutic abortion on account of diabetes	Congenital diabetes	56	Retinopathia + Nephropathia
2	B. Ö,	33	0-para Therapeutic abortion	29	68	Hypertonia + Retinopathia + Nephropathia
3	N. E.	19	0-para Therapeutic abortion	17	96	Retinopathia + Nephropathia
4	L. A.	28	0-para Early spontaneous abortion in 1952 Therapeutic abortion	18	32	Retinopathia + Nephropathia
5	I. A.	28	Caesarean section in 1950 Early spontaneous abortion in 1946 Therapeutic abortion	14	40	Difficult to regulate the diabetes
6	M. H.	27	Stillborn baby 2 early spontaneous abortions in 1954. Caesarean section, healthy female baby 3140 g	14	76	
7	I. M.	22	Stillborn baby in 1950 Caesarean section, male baby 1860 g, dead after 4 days	7	60	Difficult to regulate the diabetes especially during pregnancy
8	G. L.	26	Normal delivery in 1951 Caesarean section, healthy female baby 4650 g	1	60	
9	B. J.	22	0-para Caesarean section, healthy female baby 3240 g	12	64	Increased insulin requirement during pregnancy
10	K. S.	34	Normal delivery in 1942 Spontaneous abortions in 1944 and 1945. Stillborn baby 5000 g in 1948 Stillborn baby 3950 g	11	92	Increased insulin requirement during pregnancy
11	H. F.	43	0-para Caesarean section, healthy female baby 3130 g	21	72	

TABLE 2

Glycogen and water content of placentas from diabetic mothers.

No.	Days of pregnacy	Wet weight of placenta g	% water	Mg glycogen per g dry placenta
1	70	7.5	86.8	29.80
2	90	21.0	85.7	12.65
3	100	26.9	86.6	21.80
4	101	50.0	89.4	24.40
5	121	78.0	88.8	25.13
6	219	755.0	81.7	11.30
7	235	330.0	81.4	13.55
8	245	820.0	84.6	14.00
9	247	720.0	84.2	10.00
10	250	430.0	81.0	8.13
11	251	625.0	86.4	10.00

Full term placentae of non-diabetic mothers were found to have an average glycogen content of 3.32 mg per g dry placenta with a range of 1.24 to 5.53 mg. The placentae of the diabetic mothers at full term had a significantly higher content of glycogen or 8.13 to 14.0 mg per g dry placenta. As indicated in Fig. 1 the placental glycogen content in diabetic mothers in early pregnancy seemed to be higher than in the placentae of non-diabetic mothers at the same stage of gestation. However, this difference of glycogen content in the placentae of early pregnancy is not statistically significant (Tables 2, 3 and 4). The highest value of 35.7 mg per g was found in a mother with severe pulmonary tuberculosis. The reason for this high value is not known.

The placental water content was the same in the diabetic and the non-diabetic mothers (Tables 2, 3 and 4).

Discussion

This study has shown that the glycogen content in full term placentae of diabetic mothers is higher than in those of non-diabetic mothers. As five of the six diabetic mothers investigated were delivered by Caesarean section it might be assumed that either the elimination of labour or the fact that the placenta after a Caesarean section might be frozen within a shorter time interval were possible reasons for this difference. However, three of the non-diabetic mothers were delivered by Caesarean section and the glycogen content of their placentae fell within the range of non-diabetic mothers with normal delivery. Furthermore, the time interval between

TABLE 3

Glycogen and water content of early placentas from non-diabetic mothers.

Days of pregnancy	Wet weight of placenta (g)	% water	Mg glycogen per g dry placenta
65	60	89.2	23.4
88	60	86.0	20.5
88	65	87.3	11.8
90	37	89.8	35.7
90	45	91.1	13.1
102	135	88.2	10.2
103	20	89.0	16.7
109	65	90.0	9.8
116	140	88.4	13.1
117	120	87.1	12.4
117	170	86.8	9.3
120	93	88.1	12.4
124	75	89.2	13.2
129	160	86.0	6.4
131	120	87.0	10.6
132	113	85.2	10.0
132	155	88.2	10.5
133	210	89.2	10.9
134	125	87.6	9.7
135	90	86.7	11.5
136	130	86.9	11.4
136	117	87.4	7.6
138	135	87.4	9.8
139	95	88.4	13.8
142	160	87.2	9.5

TABLE 4

Glycogen and water content of full-term placentas from non-diabetic mothers.

	Wet weight (g)	% water	Mg glycogen per g dry placenta
Men value of 16 full-term placentas	515	82.7	3.32
Range values	400–850	81.1–85.2	1.24–5.53

delivery and freezing of the placentae seemed to be of less importance as the biological half-life of glycogen in the placenta was about 2 hours, equal in the placentae of diabetic and non-diabetic mothers.

In vitro experiments have shown that early placentae have a greater ability to synthesize glycogen than full term placentae (Villee, 1953a), probably due to a diminished enzymic activity at full term. As the placentae of diabetic mothers have a higher glycogen content it might be assumed that they are more immature than placentae of normal mothers and that their enzymic activity has not yet decreased to the same extent.

Insulin has been shown to increase the enzymic activity of human placentae in vitro (Villee, 1953a). Since the diabetic patients in this study were all well controlled there seemed to be no reason to assume that the exogenous insulin might stimulate the enzymic activity of the placentae.

It has been shown that placentae from diabetic mothers do not show any macroscopical or histological differences from those of non-diabetic mothers (Warren & Le Comte, 1952). However, in cases of embryopathia diabetica the placentae are often oedematous with several infarcts and calcium incrustations. None of the infants of this study had any signs of embryopathia and all the placentae were macroscopically normal.

High glycogen content in the liver and heart of infants of diabetic mothers has been reported by Miller (1956). The liver of these infants has also a much lower activity of the tyrosine oxidizing system (Arnold, Strindberg & Zetterström, 1956) than in infants born to normal mothers. In this respect they resemble immature infants (Kretchmer, Levine, McNamara & Barnett, 1956). If the high placental glycogen content in diabetic mothers found in this study has anything to do with the changes in the foetal liver is unknown, but both findings seemed to indicate some retardation of foetal development.

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Summary

The glycogen content of placentae from diabetic mothers has been investigated. At full term the glycogen content was significantly increased with a percentage value of 0.8–1.4 as compared to the normal of 0.1–0.6. The explanation for this increase may be a retardation of placental development in the diabetic mother.

Le taux de glycogène du placenta de mères diabétiques.

Le taux de glycogène du placenta de mères diabétiques a été examiné. Lorsque la femme est à terme, le taux de glycogène est essentiellement augmenté d'un pourcentage de 0,8–1,4 en comparaison avec la normale : 0,1–0,6. L'explication de cette augmentation peut siéger dans un retard du développement placentaire chez la mère diabétique.

Der Glykogengehalt in der Placenta diabetischer Mütter.

Es ist der Glykogengehalt der Placentae diabetischer Mütter untersucht worden. Der Glykogengehalt war am Ende der Gestationsperiode erheblich gestiegen, und zwar mit einem Prozentualwert von 0,8–1,4 im Vergleich mit dem Normalwert von 0,1 – 0,6. Diese Erhöhung ist vielleicht auf eine verzögerte Placenta-Entwicklung bei der diabetischen Mutter zurückzuführen.

Contenido glicogénico en la placenta de madres diabéticas.

Se ha investigado el contenido glicogénico en la placenta de madres diabéticas. Llegado a término completo el embarazo, se ha observado que el contenido en glicógeno aumentaba significativamente con un valor por ciento de 0,8 a 1,4 comparando con la normalidad de 0,1 a 0,6. La explicación de este aumento pudiera ser un retraso desarrollo placentario en la madre diabética.

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Specific Desensitization in Bronchial Asthma in Childhood

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The first trials of specific desensitization were undertaken by Freeman and by Noon in 1911 in patients with hay fever. The method was later further developed by Cooke who in 1915 reported the result of specific desensitization of both asthma and hay fever patients. Since Salén introduced this method of treatment in Sweden about 1930, it has been used in Scandinavia to a relatively great extent, especially for asthma and allergic rhinitis.

The results reported from different sources for the treatment of asthma have varied greatly with improvement in 55–90 % (usually 70–80 %, e.g. Secher 55 %, Salén 88 %, Malmros & Rydberg 74 %, Bruun 88 %, Flensborg 83 %, Brandberg & Wilander 89 %, Henriksen 60 %, Wiholm 80 %, Colldahl 66 %). The various studies are, however, not comparable since the principles of treatment and the period of observation differ widely.

Henriksen's study is the Scandinavian investigation which has attracted most interest during recent years. He has followed 702 asthmatics of whom 90 were children. Five hundred and thirty-eight of these underwent specific desensitization and 164 served as controls. He found improvement in slightly more than 50 % after 3–6 years of observation, but no significant difference between the treated group and the control group. It is striking that the results are markedly better in the children than in the adults (68 and 57 % respectively). Control material is lacking for the group of children since only four were not treated.

One reason for Henriksen's relatively poor results is probably the short time of treatment of, as a rule, only 3–6 months. In some cases additional courses have been given after the initial therapy, and the time of treatment has in this manner been prolonged. The percentage improvement, 75 %, in the group treated longest is higher than in the total material. To what extent manifest or latent allergies were treated cannot be determined with certainty, as no exposure or provocation tests were performed and therapy was begun on the basis of skin tests only. Support for a manifest allergy against the allergen used in treatment is found in the history in some, but

not all, of the cases. A clear difference in the results between the two groups has not been demonstrated.

Follow-up studies of exclusively pediatric material have been published in Scandinavia by Flensborg, by Brandberg & Wilander and by Ryssing. Flensborg's material includes 90 asthmatic children treated with specific and nonspecific desensitization; the period of observation extended from ½ to 1½ years and the children were treated until free of symptoms for at least ½ year. No provocation or exposure tests were made, but the results of the skin tests were correlated with the history before the start of specific desensitization. In this series the improvement was given as 82%, with marked improvement in 45%. Brandberg & Wilander's investigation includes 56 children, and significant improvement was noted in 47 cases after specific desensitization. Exposure and provocation tests were not carried out here, either. Ryssing has followed 61 children with horse allergy and divided them into manifest and latent allergies. The manifest allergies have been treated with specific desensitization. In about half of these cases no manifest horse allergy could be proved after treatment. A small number of cases has served as a control material and in none of those the horse allergy has disappeared.

Flensborg has also followed about 300 asthmatic children who did not undergo specific desensitization but only received symptomatic treatment and whose exposure to allergens was decreased as much as possible. He found that the asthma had disappeared after an average of 7½ years of illness in only 40% of the children. This result contradicts the formerly common idea that most children will outgrow their asthma at puberty.

Since 1946 specific desensitization has been routinely carried out in our clinic in all suitable cases of bronchial asthma. At the beginning, the treatment was given only on the basis of the history and the results of skin tests. Exposure and provocation tests were introduced to a greater extent only a few years later. Since about 1950 the latter tests have always been performed in order to differentiate the latent allergies from the manifest ones.

Mainly for practical reasons the specific desensitization is started in the hospital, and we have used the so-called rush desensitization in which the patients receive their allergen injections in successively increasing doses every second hour during the daytime. The treatment has then been continued with a monthly maintenance dose. Most of the children have been followed in our Allergy Out-patient Clinic and only a smaller number by their local physicians. The treatment has, as a matter of principle, been continued for at least two years, and we have tried to have the patients asymptomatic, if possible, for at least one year before cessation of treatment.

It is our opinion that most of the reports hitherto published of specific

desensitization have not taken into sufficient consideration whether the allergies were latent or manifest. The significance of exposure and provocation tests for the division of allergies into manifest and latent types has been stressed by Salén & Juhlin-Dannfelt, Arner, Colldahl, Kraepelien, and others. Since there is reason to believe that the specific desensitization of manifest allergies should give better results than such treatment of latent allergies, we thought it of interest to re-examine our patients with manifest allergies who have undergone specific desensitization.

Material

We decided to re-examine all the 113 asthmatic children who were admitted to the Pediatric Department, Karolinska Sjukhuset, Stockholm, during the period 1 July 1951 to 30 June 1953 and who received specific desensitization therapy. This period was chosen with the thought that exclusively manifest allergies were treated then, and at the same time the longest possible period of observation could be obtained. The observation period has been a maximum of four years and a minimum of two years since the beginning of treatment.

We were able to contact 110 of the 113 children for follow-up examination in the fall of 1955. The great majority of the children were examined and questioned by us personally. A smaller number were contacted only by telephone and information about a few was gathered from their local physicians.

The age distribution of the material is shown in Fig. 1. Most of the children are between 5 and 10 years of age. The sex distribution is the usual one for asthma.

The degree of working capacity is used in the classification of asthma in adults.

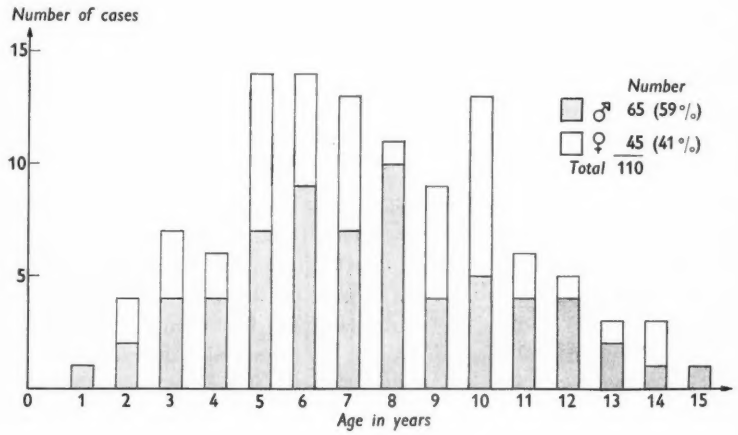

Fig. 1.

TABLE 1

Classification of asthma.

Group		Number of cases
1	Mild asthma with less than 5 short attacks per year	34
2	Medium severe asthma with 5–10 attacks per year	45
3	Severe asthma with more than 10 attacks per year or prolonged status asthmaticus	31
Total		110

This classification is not applicable to children and therefore we chose to divide our material into three groups according to the frequency of attacks. This ought to be a relatively good index of the degree of severity. Table 1 shows the basis for the division into the groups and also indicates that the material is quite evenly distributed among them.

Ninety-one cases (83 %) were pure inhalation allergies, 2 cases (2 %) were pure food allergies and 17 cases (15 %) were combined food and inhalation allergies. It appears that food allergies do not play an important part in childhood asthma, at least not sufficient to require specific desensitization. The most common inhalation allergies are, in order of frequency, tree and timothy pollen, house dust and horse epithelium.

Results

It is evident from the material that no difference is found between boys and girls in the severity of the disease. Allergic heredity is present in 71 cases (65 %). Eczema is or was found in 73 cases (66 %). These latter factors do not affect the severity, nor does the duration of the asthma influence it. The age of onset, on the other hand, is shown to be of some importance, as can be seen from Table 2. The more severe the asthma is, the earlier is the onset.

We considered it of greatest interest to correlate the results with the severity and the duration of the asthma and with the duration of therapy. The results have been classified into 6 groups: asymptomatic, markedly improved, improved, unimproved, worse, and dead. We consider a patient "asymptomatic" if he has been completely without complaints for at least one year at the time of re-examination. By "markedly improved" we mean that the patient was free from attacks for at least the last year but had slight symptoms of asthmatic bronchitis with respiratory infections and/or slight respiratory difficulty on exertion. "Improved" means that the frequency and intensity of attacks have decreased markedly.

TABLE 2

Severity of asthma in relation to age of onset.

Degree of severity	Number of cases	Age of onset		
		0 – 2 years	3 – 5 years	6 – 12 years
Group 1	34	9 (27 %)	14 (41 %)	11 (32 %)
Group 2	45	22 (49 %)	15 (33 %)	8 (18 %)
Group 3	31	18 (58 %)	11 (36 %)	2 (6 %)

Table 3 shows that improvement occurred in 84 % of the total material. If only the "asymptomatic" and "markedly improved" categories are considered, the figure is 71 %. No difference in the results of treatment can be demonstrated between Group 1 (mild asthma) and Group 2 (medium severe asthma). Clearly worse results are noticed in Group 3 which is composed of children with the most severe asthma.

The only death was a 3-year-old boy with very severe asthma and polyvalent hypersensitivity, particularly a massive hypersensitivity against horse epithelium. He died in status asthmaticus nearly two years after the start of therapy.

A direct effect of the duration of asthma on the result cannot be definitely proved from the investigation. Only a tendency to worse results with early age of onset is observed, but this may be connected with the make-up of Group 3 which contains more children in whom the asthma began early than the other groups do.

We have separated the children into two groups according to the duration

TABLE 3

Results in relation to severity of asthma.

Result	Degree of severity						Total	
	1			2				
Asymptomatic	12	26	30 (88 %)	11	37	41 (91 %)	28	78
Markedly improved	14	(76 %)		26	(82 %)		5	15
							10	(48 %)
								21 (68 %)
							50	(71 %)
								92 (84 %)
Improved	4			4			6			14	
Unimproved	1			3			8			12	
Worse	3			1			1			5	
Dead	–			–			1			1	

TABLE 4

Results in relation to duration of therapy.

Result	Duration of therapy			
	less than 2 years		2 – 4 years	
Asymptomatic	3		25	
Markedly improved	5	10 (56 %)	45	82 (89 %)
Improved	2		12	
Unimproved	7		5	
Worse	1		4	
Dead	–		1	

of treatment for correlation of this factor with the results: those treated for less than 2 years and those with treatment of 2–4 years (see Table 4). The limit was set at two years, since a difference in the results of therapy was noted just at that time. The first group is relatively small, which makes comparison uncertain. The difference is, however, so great that the results can be said to be worse with short treatment.

One might have expected a decrease in the frequency of improvement in the group which was observed four years in comparison with the group observed only two years. One difference between these two is that the two-year group is for the most part still under treatment, while the four-year group has, in most cases, finished treatment 1–2 years ago. No difference could be demonstrated between the two groups.

Neither the presence of an allergic heredity nor the occurrence of eczema affects the results. A tendency to poorer results can be noted when the desensitization is undertaken with more than a few allergens. In view of the limited size of the material, it was felt that no analysis could be made on basis of the allergens used.

Discussion

As stated earlier, comparison between different materials is difficult. Nevertheless the importance of specific desensitization must become evident when our results are compared with the results from Flensborg's material of asthmatic children, who did not receive such treatment.

We have also been able to show better results than Henriksen reported for children. The cause for this is probably the significantly longer duration of therapy. Our results agree in general with Flensborg's and with those of Brandberg & Wilander. These authors have, however, observed their ma-

TABLE 5

Additional therapy in connection with specific desensitization.

Result	Number of cases	Elimination of foci of infection		Anti-catarrhal vaccination		ACTH or cortisone	
Asymptomatic	28	6	16	1	3	1	6
Markedly improved	50	7		1		3	
Improved	14	3		1		2	
Unimproved	12	1		2		3	
Worse	5	1		1		2	
Dead	1					1	

terial for a shorter period and the children in Flensborg's material have also been the object of nonspecific desensitization concurrent with the specific therapy.

Although the results reported here can be looked upon as very good, they can naturally not be attributed solely to the specific desensitization. General measures, consisting of the most complete possible elimination of the exciting allergens, have been carried out in all cases and adequate symptomatic therapy has been given in addition.

There is another factor of significance in a chronic disease like asthma with its considerably psychogenic component. This is the monthly control and the possibility of constant contact with the hospital and the attending physician, and the favorable effect of this should not be underestimated.

As can be seen in Table 5, foci of infection were eliminated or anti-catarrhal vaccination was carried out in connection with the specific desensitization in a smaller number of cases. Altogether ten patients received ACTH or cortisone at some time during the course of treatment; six of these belong to the "improved" group. In three such cases, the favorable course of the asthma can probably be ascribed to the hormonal therapy.

We have no control material of our own with identical treatment but without specific desensitization. We have not felt able to run such a control series for humanitarian reasons, since we feel that adequate therapy must be started as early as possible in order to save the children additional inconveniences and to prevent the development of pulmonary changes.

As long as such results cannot be reached in another manner, specific desensitization should be done for manifest allergies in which satisfactory allergen elimination is not possible in spite of the disadvantages connected with such treatment—especially in children.

Summary

1. One hundred and ten asthmatic boys and girls in the ages 1–15 years with manifest allergies who underwent specific desensitization have been followed for 2–4 years after the onset of treatment.

2. Improvement was noted in 84 %; if only absence of symptoms and significant improvement are included, the figure is 71 %.

3. The duration of asthma has no evident effect on the result.

4. The duration of treatment is of importance for the result. The longer and the more intense the therapy, the better are the results registered.

5. The results are the same for children observed two years as for those observed four years.

6. The significance of specific desensitization for manifest allergies in asthmatic children is stressed.

Désensibilisation spécifique des enfants asthmatiques.

Cent dix cas de garçons et de filles asthmatiques à l'âge de 1–15 ans avec allergie manifeste ont été soumis à une désensibilisation spécifique et examinés 2 à 4 ans dès le commencement du traitement. Une amélioration a été constatée dans 84 % des cas. Le chiffre s'élève à 71 % si on inclut seulement les améliorations significatives ou l'absence de symptômes. La durée de l'asthme n'a pas d'effet évident sur les résultats du traitement. La durée du traitement est importante pour le résultat. Un traitement plus long et plus intense donne de meilleurs résultats. Les résultats sont les mêmes pour les enfants observés pendant deux ans comme pour ceux observés pendant quatre ans. L'importance de la désensibilisation spécifique pour des allergies manifestes dans des enfants asthmatiques est mis en évidence.

Spezifische Desensibilisierung von asthmatischen Kindern.

Einhundertzehn asthmatische Knaben und Mädchen im Alter von 1–15 Jahren mit manifesten Allergien, die spezifischer Desensibilisierung unterzogen wurden, sind 2–4 Jahre nach dem Ansetzen der Behandlung verfolgt worden. Besserung wurde bei 84 % beobachtet; bei Forderung von Symptomfreiheit und signifikanter Besserung beträgt die Zahl 71 %. Die Dauer des Asthmas hat keinen augenfälligen Einfluss auf den Erfolg. Die Dauer der Behandlung ist von Bedeutung für das Resultat. Je länger und je intensiver die Therapie ist, umso besser sind die erzielten Erfolge. Bei den zwei wie bei den vier Jahre lang nachuntersuchten Kindern wurden dieselben Resultate beobachtet. Die Bedeutung der spezifischen Desensibilisierung bei asthmatischen Kindern mit manifesten Allergien wird betont.

Desensibilización especifica de los niños astmáticos.

Ciento diez niñas y niños asmáticos entre 1 y 15 años de edad, con alergía manifiesta fueron estudiados durante un período que osciló entre 2 y 4 años desde el comienzo del tratamiento desensibilizante. En el 84 % de los casos se anotó mejoría manifiesta. La cifra es del 71 % si se tiene en cuenta sólo la ausencia de síntomas y una mejoría significativa. La duración de la enfermedad, asma, no mostró influenciar los resultados.

La duración del tratamiento tiene importancia en los resultados: Cuanto mas larga e intensa la terapeútica mejores fueron estos. No se encontró diferencia en los resultados al cabo de dos y de 4 años. Se enfatiza la significación del tratamiento desensibilizante en las alergías manifiestas de niños asmáticos.

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Housing Conditions and Child Morbidity

Relation of Different Housing Factors to Hospitalisation Rate of Children

by VAGN CHRISTENSEN

Various investigations have been made during the past 70 years into the significance for health of housing conditions. These investigations gave the concordant results that children especially are susceptible to the influence of bad housing, and that in this age group particularly infectious diseases increase in frequency and severity under bad housing conditions.

The property of the residence used by previous observers as a basis for assessing the influence has been either the size of the dwelling (Carnally *et al.*, 1887; Russel, 1888; Chalmers, 1913; Bergman, 1939; and others) or the household density, i.e. the number of persons per room (Woodbury, 1925; Stocks, 1934; Joensen, 1954; and others). A few workers have based their investigations on an evaluation of the quality of the dwelling and thereby found that this factor, too, seems to be of importance (Rietz, 1930).

Hardly any of the previously reported studies include an attempt to distinguish between the effects of different properties of the residence. This question must be of considerable interest from a practical hygienic point of view. The objects of the present study were therefore to investigate whether a relationship exists between morbidity rate and housing conditions in a modern society with a well-organized combating of diseases, and, further, to try to clarify which properties of the dwelling are of chief importance in respect to health.

Material

Residential areas.—(1) About 10,000 flats situated in the oldest and worst slum quarters of Copenhagen, examined and assessed with regard to quality by the Municipal House Inspection and Condemnation Board with a view to possible condemnation.

(2) The district of Emdrup, a fairly new and hygienically satisfactory residential area comprising approximately the same number of persons.

Children.—All children under 7 years of age in the stated residential areas, counted

at the census in 1950, grouped according to size of dwelling, quality of house, and household density (number of persons per room).

Hospitalized children.—Admissions from the above residential groups within the period of 1948–1952 of children under 7 years of age. The material was collected from so many Copenhagen hospital units that practically all admissions of children from the examined areas must be supposed to have been included in the investigation. Excluded were children admitted to surgical units.

Procedure.—On this basis a comparison was made between the admission rates under different housing conditions. The justification of this procedure was tested by comparing the same residential areas, partly on the basis of a review of death certificates and partly on the basis of home visits, giving information on the morbid conditions treated at home in the two areas.

Results

A comparison of the admission rates under different housing conditions revealed very considerable qualitative as well as quantitative differences between the patients from good and bad residential areas respectively. The qualitative differences are described in detail elsewhere (Vagn Christensen 1956a and b). Hence, only the most important results will be recapitulated here.

(*a*) *Comparison of the Children Admitted from a Good and a Bad Residential Area*

Tables 1*a* and *b* give some general information concerning the patients admitted from each of the two residential areas examined. In Table 1*a* are set out the number of children living in each area, the number of admissions, and the number of children admitted. In addition, the admissions per 1000 children living in each area has been calculated. Table 1*b* shows the number of births, as well as the number of deaths within the period of investigation among infants under 1 year of age in each area. The infant mortality was calculated on the basis of these figures.

It is seen that the material from the bad residential area comprised 2844 children, of whom 1484 had been admitted altogether 2169 times within the 5-year period of investigation. The material from the good residential area comprised 2236 children, of whom 599 had had a total of 813 admissions. Calculated per 1000 children, 522 from the bad area had been in hospital within the period of investigation and 269 from the good, i.e., about twice as many from the former as from the latter. The number of admissions was likewise twice as high from the bad residential area as from the good, 763 and 364 respectively per 1000 children in each area.

The differences as regards admissions to hospital from the two residential areas correspond closely to differences in infant mortality. Table 1*b* shows that the mortality within the first year of life (per 1000 live births) was 42 per mille in the bad area against 21 per mille in the good.

TABLE 1*a*

The material from the two residential areas.

The number of children living in each area, the number of admissions, and the number of admitted children. In addition, the number of admissions and of admitted children per 1000 children in each area. The ratio between the admission rates from the two areas.

	Bad area	Good area	Bad area/Good area
No. of children	2,844	2,236	
No. of admissions	2,169	813	
No. of admitted children	1,484	599	
Per 1000 children living in each area:			
No. of admissions	763	364	2,1
No. of admitted children	522	269	1.9

TABLE 1*b*

Calculation of the infant mortality in the examined areas.

The number of births in each area, the number of deaths of infants under 1 year of age, and the number of deaths per 1000 births. The ratio between the two areas.

	Bad area	Good area	Bad area/Good area
No. of births	1,925	1,236	
No. of dead under 1 year of age	81	26	
Infant mortality	42	21	2

It must be remarked that neither the admission rate nor the mortality rate fully express the actual morbidity under bad housing conditions. The investigation reported elsewhere (Vagn Christensen, 1956a and b), based on home visits in the residential areas here examined, revealed that the difference of the admission rate from the good and the bad area was as 1 to 2 or 1 to 4, whereas the ratio between the numbers of children with proper diseases treated at home was as 1 to 9.

The higher admission rate found here from the bad residential area was not uniformly distributed over various groups of diseases. Apparently the diagnoses may be grouped as follows:

(1) Almost equal admission rates from the two residential areas were found for poliomyelitis, tuberculosis, nervous disorders, convulsions, maladjustment, oligophrenia and scarlet fever.

(2) About twice as many admissions from the bad area as from the good

were noted in the cases of upper respiratory infections, asthma, enuresis and encopresis, constipation, chronic dyspepsia, prematurity, congenital malformations and congenital debility, rickets, and anaemia.

(3) For a group of severe infectious diseases the admission rate was 3 or 4 times higher from the bad area than from the good: bronchitis and pneumonia, otitis media, measles, pertussis, ac. dyspepsia, meningitis, and burns.

(4) The number of admissions due to skin diseases was 5 to 9 times greater from the bad area than from the good.

These differences between the admission rates from the two residential areas are presumably in general accountable for by different conditions of living in the two environments. It is hardly possible to state exactly to which extent the individual environmental factors, among which the dwelling, are responsible for the results achieved. There is, however, reason to suppose that the diesases mentioned in items 3 and 4 are to the greatest extent influenced by such factors as crowding, damp air and absence of sunlight. The incidence of these diseases may therefore probably be regarded as a direct expression of the effect of the housing conditions.

Further comparison of the two groups showed that the difference in admission rate was the greatest for infants of the youngest age group, a fact which involves a rather considerable difference between the age distributions of the two series of hospitalized children. Finally, a rather considerable difference was noticed with regard to breast-feeding. A smaller proportion of those from the bad residential area had been breast-fed compared with those from the good area, and of those who had, the great majority had ceased sooner, so that among infants over 3 or 4 months of age breast-feeding was twice as frequent in the good as in the bad area.

Thus, there are very considerable qualitative differences between the children admitted to hospital from good and bad housing conditions. In the present investigation the residential groups described below were also analyzed with a view to these differences. The results were in close agreement with those achieved by comparing the two residential areas collectively. Below I shall therefore deal solely with the purely quantitative differences between the admission rates under different housing conditions.

(*b*) *The Significance of Different Properties of the Residence*

The size of the dwelling

Table 2 shows the material from the good and the bad residential area, grouped according to the size of the dwelling. The table shows the number of children and the number of admissions for each size of dwelling in each area. On the basis of these figures has been calculated the admission rate

TABLE 2

Number of children and number of admissions for each size of dwelling in each of the examined areas.

Calculated admission rate per 100 children in each residential group, partly for the whole period of investigation and partly annually.

Size of dwelling	Bad area				Good area			
	Child.	Adms.	Adms. per 100 children		Child.	Adms.	Adms. per 100 children	
			Whole period	Annually			Whole period	Annually
1 room	152	239	158	31.6	30	18	60	12
2 rooms	1,825	1,388	76	15.2	1,140	493	43	8.6
3 rooms	581	369	64	12.8	460	146	32	6.4
4 rooms and over	286	133	47	9.4	606	137	23	4.6
not stated		40				19		
Total	2,844	2,169	77	15.4	2,236	813	36	7.2

per 100 children in each residential group, partly for the entire 5-year period and partly annually.

The table plainly shows a relationship between the size of the dwelling and the admission rate. It is seen that in the bad residential area the annual admission rate from one-, two-, three- and four-room dwellings was about 32, 15, 13, and 9 per cent respectively. In the good area the corresponding figures were about 12, 9, 6, and 5 per cent. The importance of the environments of the dwelling is likewise obvious. For each size of dwelling the admission rate from the bad area was about twice as high as that from the good area.

TABLE 3

The material from the area examined by the Board.

Number of children and number of admissions by size of dwelling and quality of house. Absolute figures.

Size of dwelling	Quality I		Quality II		Quality III		Quality IV		Total	
	Child.	Adms.	Child.	Adms.	Child.	Adms.	Child.	Adms.	Child.	Adms.
1 room	43	60	68	112	23	31	18	35	152	238
2 rooms	116	103	579	501	601	461	529	323	1,825	1,388
3 rooms	34	28	199	161	198	137	150	43	581	369
4 rooms and over	5	9	23	25	121	39	137	60	286	133
Total	198	200	869	799	943	668	834	461	2,844	2,128

TABLE 3*a*

Admission rate per 100 children in each residential group, calculated on the basis of Table 3.

Size of dwilling	Quality I	Quality II	Quality III	Quality IV	Average
1 room	140	165	135	194	158
2 rooms	89	87	77	61	76
3 rooms	83	81	69	29	63
4 rooms and over .	180	109	32	44	47
Average	101	92	71	56	75

The quality of the house

In Table 3 the material from the bad area examined by the Municipal House Inspection and Condemnation Board has been grouped according to size of the dwelling and quality of the house. It shows the number of children and the number of admissions for each residential group. Quality I comprised houses scheduled for immediate demolition, Quality II houses scheduled for demolition within a short span of years, the majority within 10 to 25 years, Quality III improvable houses, and Quality IV satisfactory houses according to existing legislation and practice. The admission rate per 100 children in each residential group within the 5-year period of investigation has been calculated on the basis of these figures (Table 3*a*).

These tables illustrate the significance of the size of the dwelling and of the quality of the house. The importance of the size of the dwelling is most conspicuous in the houses of the best qualities (III and IV). Thus, for instance, the admission rates from dwellings with one, two, three, and four or more rooms of Quality IV were 194, 61, 29 and 44 per cent respectively. Likewise the quality proved to play the greatest part for the large dwellings. Thus, the admission rates from four-room dwellings of Qualities I, II, III, and IV were 180, 109, 32, and 44. This may be due to the fact that the absolute number of children is relatively small in some of the groups, but the figures may also suggest that only when one property of the residence is tolerably satisfactory do the influences of other factors manifest themselves.

Significance of the quarter

This was studied by comparing the satisfactory houses in the bad residential area (Qualities III and IV) with the good area, the district of Emdrup. The conditions compared here may in part be expressed by the density of

TABLE 4

Comparison of quarters: the non-condemnable houses in the bad area compared with the good area, Emdrup.

Number of children, number of admissions, and number of admissions per 100 children in each residential group.

Size of dwelling	Bad area						Good area		
	Quality III			Quality IV					
	Child.	Adms.	Adms. per 100 child.	Child.	Adms.	Adms. per 100 child.	Child.	Adms.	Adms. per 100 child.
1 room	23	31	135	18	35	194	30	18	60
2 rooms	601	461	77	529	323	61	1,140	493	43
3 rooms	198	137	69	150	43	29	460	146	32
4 rooms and over	121	39	32	137	60	44	606	137	23
Total	943	668	71	834	461	56	2,236	794	36

population (number of persons per hectare = a scant half acre). This ranged from 300 to 900 in different parts of the bad residential area, while in the good area it ranged from 50 to 100. The figures thus indicate the free space at the disposal of each person. The difference in this respect between the two areas is actually still greater than the stated figures suggest, because a large proportion of the houses in the bad area is used for business purposes, thus leaving even less free space for the residents.

In Table 4 the material from the satisfactory houses in the bad residential area (Qualities III and IV) as well as that from the good area have been grouped according to size of dwelling. We here find the number of children, the number of admissions, and the number of admissions per 100 children in each residential group. It appears that for all sizes of dwelling the admission rate was about 1½ to 2 times higher from the bad area than from the good.

Significance of the household density

By household density we understand the number of persons per room. In Danish reports the kitchen is not included as a room. For the present investigation information as regards household density was procurable only for the good area, but the examinations made in the bad area suggest that the conditions were approximately equal in this respect.

TABLE 5

The material from the good residential area by size of dwelling and household density.

The number of children and the number of admissions in each group. Absolute figures.

Household density	1 room		2 rooms		3 rooms		4 rooms and over		Total	
	Child.	Adms.	Child.	Adms.	Child.	Adms.	Child.	Adms.	Child.	Adms.
Less than 2 persons per room	0	0	409	163	456	112	489	97	1,354	372
2 persons per room	6	7	594	250	30	16	19	7	649	280
More than 2 persons per room	22	11	145	68	23	18	43	17	233	114
Not stated		0		12		0		16		28
Total	28	18	1,148	493	509	146	551	137	2,236	794

TABLE 5*a*

Admissions per 100 children in each residential group (Table 5).

Household density	1 room	2 rooms	3 rooms	4 rooms and over	Average
Less than 2 persons per room	—	40	25	20	27
2 persons per room	117	42	53	37	43
More than 2 persons per room	50	47	78	40	49
Average	64	43	29	25	35

In Table 5 the material from the good area has been grouped according to the size of the dwelling and according to whether there lived under two persons, two persons, or over two persons per room. (The statistically employed lower limit of over-populations is more than two persons per room.) We see the number of children and the number of admissions in each residential group. The admission rate per 100 children in each residential group has been calculated on this basis (Table 5*a*).

It must be remarked that the absolute figures from one-room dwellings are so small that conclusions regarding this group are very uncertain. However, the group of one-room dwelling with two persons per room comprised exclusively lonely (widowed and unmarried) mothers, a fact which presumably explains the very high admission rate within this group.

In two-room dwellings the household density seems to play an inferior part. It is seen that any household density in two-room dwellings had an admission rate of approximately the same order as larger dwellings with two or more persons per room. The conditions may, perhaps, be formulated in the way that only in three-room and larger dwellings do families with children have a chance of attaining to household densities low enough to be hygienically satisfactory. This limit seems to lie at under two persons per room. The admission rate was about half as high from three- and four-room dwellings with under two persons per room as from all the remaining residential-groups.

Summarizing we may say, on the basis of this survey of the significance of various housing factors, that several properties of the residence seem to be of hygienic importance. A 6 or 7 times higher admission rate from one-room dwellings in the bad residential area than from four-room dwellings in the good area constituted the maximum difference. This very great difference resulted from a total influence on the admission rate especially of the size of the dwelling and the quarter, i.e., an influence of the space at the disposal of the individual child. The result of the investigation into the significance of the household density should probably be assessed in the same way. The quality of the house also plays an important part under otherwise uniform conditions, though the influence of this factor seems not to manifest itself till the most elementary requirements regarding space have been fulfilled.

The materials from the individual residential groups were examined with a view to the qualitative differences, as previously stated. The results were the same as that achieved by comparing the two areas collectively: an excess of admissions form the bad residential groups compared with the good was found especially for infants within the first year of life, the majority suffering from infectious diseases and skin diseases (Vagn Christensen 1956a).

Discussion

In relation to the account of the qualitative differences found by comparing the children admitted from a good and a bad residential area it was mentioned that these differences were too great to be due exclusively to the housing conditions. Within certain groups of diseases it seems reasonable to regard the results as an effect on the mothers of the, in many respects, unfortunate environmental conditions prevailing in bad residential areas, e.g. such affections as prematurity, congenital debility, congenital malformations, and possibly enuresis, encopresis and constipation.

It is hardly possible to give an account of all the environmental differences with which one works in comparing different residential groups. The investigation reported here included, as far as possible, information on other environmental factors that might be supposed to influence the morbidity and admissions of children to hospital (Vagn Christensen 1956a).

It appeared that children of lonely mothers constituted a considerably larger proportion of the hospital material from the bad residential groups (25 per cent of the admissions), than of that from the good groups (9 per cent of the admissions), and that the offspring of lonely mothers seemed, under otherwise uniform conditions, to have a higher admission rate than the offspring of married couples. This doubltless accounted in part for the observed higher admission rate from the bad residential groups than from the good, but it cannot alone explain the differences found.

Various investigations have revealed higher morbidity and mortality rates in the lowest social classes compared with the higher ones. In the present material the admission rates from the different social classes seemed to be approximately equal under good housing conditions, whereas under bad housing conditions there were far more admissions of children belonging to the working classes. In residential groups which apparently were rather uniformly composed with regard to the social position of the wage earner, the influence of the dwelling on the admission rate nevertheless seemed to be marked. The influence of the housing conditions on the admission rate thus seems to be primary to that of the social position.

Similarly a study of the average income in the different residential groups showed that a high income coincided in the main with good housing and a low income with bad housing; but in cases of uniform incomes the admission rate seemed to depend largely on the housing conditions.

Further investigations into various environmental conditions in the two residential groups showed that the number of mothers with full-time jobs away from home and the number of children sent to day nursery or kindergarten probably were somewhat greater in the bad residential area than in the good. This was presumably mainly due to the fact that the greatest number of lonely mothers lived in the bad residential area. Among children of married wage earners there was no appreciable difference between the two areas. These facts therefore cannot either explain the results achieved.

Nutritional factors are likewise unlikely to be responsible. The nutrition may to some extent be qualitatively insufficient in the worst residential groups, a fact which may have had a certain influence on the high admission rates from these groups. However, variations in the admission rate dependent on the housing conditions were found in all the groups, even in several groups where nutritional differences are unlikely to have played any part.

Regarding this question there is reason to point out that infectious diseases and skin diseases are mainly responsible for the difference in admission rate between different residential groups. These diseases are hardly in any marked degree due to malnutrition. Other diseases, which might be supposed to be more intimately related to malnutrition (e.g. anaemia and rickets) showed smaller variations between the different residential groups. Finally, the differences between admissions of breast-fed infants from different residential groups were of the same order as the remaining differences found in the material.

The question may be raised whether the groups of population here examined are comparable at all. Especially it is worth considering whether the children in the different residential groups receive the same care. There is reason to suppose that they do not. Various observers (Joensen, 1954; Spence *et al.*, 1954) have demonstrated a relationship between bad housing conditions and bad care of the children. Spence *et al.* even found a causative relation, having in some instances observed that improvement of the housing conditions was followed by better care of the child. There is no doubt that this causative relation plays an essential part in the unquestionable differences seen with regard to the care of the children when comparing different housing conditons. Whether, in addition, personal, and possibly constitutional qualities of the examined groups of population have any appreciable influence on the results achieved is presumably in the end a matter of opinion. No objective basis seems available for a knowledge concerning this problem.

Summary

The present investigation was carried out as a comparison of the percentage admissions to hospital of children under different housing conditions. The properties of the residence that were examined were as follows: size of dwelling, quarter, quality of house, and household density (number of persons per room).

The investigation revealed considerable qualitative as well as quantitative differences between the materials from good and bad housing conditions respectively. Under bad housing conditions there was found an increased admission rate compared with that under good conditions, expecially within the first 2 or 3 years of life, and particularly owing to infectious diseases, burns and skin diseases.

"Bad housing conditions" seem to prevail where there is too little space for the inmates. Thus, there was found a raised admission rate (1) from one- and two-room dwellings compared with larger dwellings, (2) from densely built-over and densely crowded quarters compared with quarters having more free space, (3) from dwellings with two or more persons per room compared with dwellings with under two persons per room. (4) Finally, the quality of the house also seems to play a part, especially when the most elementary requirements with regard to space have been fulfilled.

The influences of various other environmental factors on the admission rate were likewise investigated. Of these, especially the familial position of the wage earner

(lonely mothers) seems to influence the admission rate, whereas the importance of the dwelling seems to be primary to that of the social position and income.

Conditions de logement et morbidité enfantile. Relation des différents facteurs de logement avec la fréquence d'hospitalisation des enfants.

Comparaison du pourcentage des hospitalisation d'enfants sous diverses conditions de logement. Les propriétés de la résidence, qui ont été examinées, sont les suivantes : dimensions du logement, quartier, qualité de la maison et importance de la famille (nombre de personnes par chambre). Les recherches ont révélé de considérables qualités tout comme des différences quantitatives dans le matériel recueilli à propos des logements respectivement bons ou mauvais. Lors de mauvaises conditions de logement, on a constaté une augmentation du nombre des admissions à l'endroit de ce nombre lors de bonnes conditions, spécialement dans les 2 ou 3 premières années de vie; cette augmentation doit être attribuée en particulier à des maladies infectieuses, des brûlures et des maladies de peau. Les mauvaises conditions de logement semblent prévaloir quant il y a trop peu d'espace pour tous les membres de la famille; la qualité du logis semble aussi jouer un rôle surtout quand les exigences les plus élémentaires quant à l'espace ont été remplies. La position familiale du chef de famille (mères seules) semble elle-aussi influencer la norme d'admissions, tandis que l'importance du logement semble surpasser celle de la position sociale et du reveny.

Wohnungsverhältnisse und Kindermorbidität. Das Verhältnis verschiedener Wohnungsfaktoren zu der Krankenhausaufnahmezahl von Kindern.

Ein prozentualer Vergleich der Krankenhausaufnahmen von Kindern unter verschiedenen Wohnungsverhältnissen. Folgende Faktoren der untersuchten Häuser wurden berücksichtigt: die Wohnungsgrösse, die Lage, die Qualität der Wohnung und die Haushaltsdichte (Anzahl Personen pro Zimmer). Bei der Untersuchung stellten sich erhebliche qualitative wie auch quantitative Unterschiede zwischen den Fällen aus guten bzw. schlechten Wohnungsverhältnissen heraus. Es wurde festgestellt, dass sich die Aufnahmezahl der Kinder unter schlechten Verhältnissen steigerte gegenüber der Zahl unter guten Verhältnissen, vor allem innerhalb der ersten 2 oder 3 Lebensjahre und dann besonders infolge Infektionskrankheiten, Verbrennungen und Hautkrankheiten. Schlechte Wohnungsverhältnisse scheinen dort vorzuherrschen, wo entsprechend der Anzahl der Bewohner zu wenig Raum vorhanden ist; auch die Qualität des Hauses scheint eine Rolle zu spielen, auch wenn den elementarsten Anforderungen hinsichtlich des Raumes entsprochen wird. Ferner scheint der Familienstand des Ernährers (alleinstehende Mutter) die Aufnahmezahl ebenfalls zu beeinflussen, wobei die Wohnung von grösserer Wichtigkeit zu sein scheint alls die soziale Stellung und das Einkommen.

Condiciones de alojamiento y morbosidad infantil. Relación entre los diversos factores correspondientes al alojamiento y relativas proporciones de hospitalización infantil.

Se compara el porcentage de ingresos en el hospital de niños bajo diferentes condiciones de alojamiento. Se examinaron como sigue las diversas conveniencias con respecto al domicilio: tamaño de la vivienda, barrio, calidad de la casa y densidad de los habitantes (número de personas por habitación). La investigación reveló cualida-

des considerables aste como diferencias cuantitativas de las condiciones materiales, de satisfactorias a francamente malas respectivament. Bajo las malas condiciones se comprobó una proporción aumentada de ingresos en el hospital comparativamente con las buenas condiciones, especialmente tratándose de los 2 a 3 primeros años de la vida, y particularmente debido a enfermedades infecciosas, quemaduras y enfermedades cutáneas. Las malas condiciones del vivir parecen prevalecer donde existe demasiado poco sitio para los moradores; la calidad de la casa también parece desempeñar un papel, especialmente cuando los más elementales requisitos referente al sitio disponible han sido satisfechos. La posición del sostén de la familia (madres solitarias) también parece influir en la proporción de hospitalizaciones, mientras la importancia del domicilio propiamente dicho parece superponerse a la de la posición social y los medios monetarios.

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Adolescent Mortality in The Netherlands

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". . . the elimination of all but a few deaths at young adult ages is surely a reasonable objective of preventive and curative medicine"—R. C. GEARY, 1952.

1. Introduction

Within the range of an analysis of child mortality according to age groups (de Haas, 1956) and in connection with an investigation on the development and state of health of adolescents, which is going on in our department, the present paper will give a survey of the trends in adolescent mortality over the past fifty years. Special emphasis is laid on the *rapid* changes which have taken place after the second world war.

Both in Dutch and foreign publications reports on adolescent mortality are scanty. In order to pave the way to efficient medical care for adolescents it is necessary to fill this gap. Mortality rates for adolescents have always been comparatively low (only school children, as a group, show a lower mortality), so that unlike infant mortality rates, for example, they did not demand a further analysis (Fig. 1).

The trends in mortality rates together with changes in the pattern constituted by the various causes of death reflect the changes which have come about and present-day conditions. This does not imply that rates of mortality give us sufficient information about the morbidity of this group, but as a rule they are an indication of what diseases and accidents are of major importance. Thus one fatal traffic accident means about 20–50 road accidents in which the victim needs medical treatment.[1] Moreover an analysis of mortality rates reflects socio-medical conditions.

[1] Calculated from figures given in *Statistics of Traffic Accidents*, 1951, Central Bureau of Statistics, The Hague.

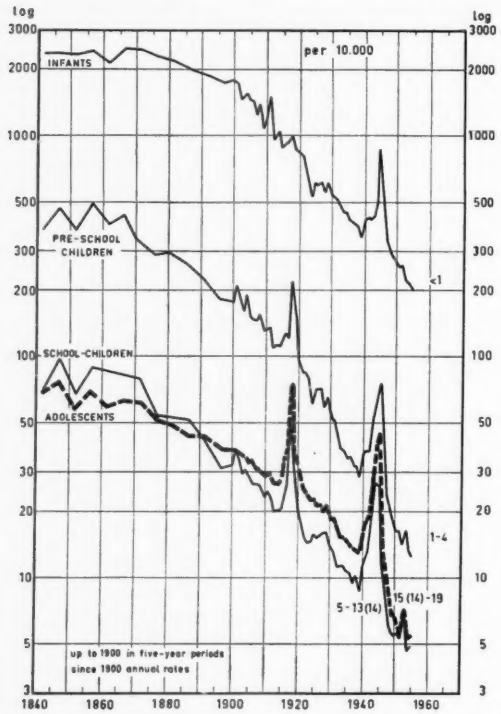

Fig. 1. Child mortality in The Netherlands, 1840–1955.

Adolescents are defined, in agreement with international usage in mortality tables, as boys and girls from *15* up to and including 19 years of age.

Up to and including 1920 the available data cover the age group of *14* up to and including 19 years. The mortality rates of 14-year olds are slightly lower than those of the age group from 15–19, so that the rates from 1900 to 1920 (calculated on an age group from 14 to 19 years) are proportionately a little too low (Chassagne). This difference, however, is very slight.

The number of adolescents between 15 and 19 years increased during the period 1900–1940 from 500,000 to well over 800,000—almost 10 per cent of the total population. At present the figure would be about $7\frac{1}{2}$ per cent (818,000). This percentage is likely to increase from 1960 onwards, when the high post-war birth rates will make themselves felt.

The total adolescent mortality is stated per *ten* thousand, the mortality tabulated according to cause of death per *hundred* thousand of this age group.

TABLE 1

Adolescent mortality in The Netherlands 1901/04 to 1950/54 per 10,000.

Period	Total mortality	♂	♀
1901/04	35.9	36.2	35.6
1905/09	31.3	31.3	31.6
1910/14	27.8	27.6	27.9
1915/19	40.8	40.0	41.7
1920/24	25.5	25.4	25.6
1925/29[1]	21.2	21.6	20.8
1930/34[1]	16.8	17.8	15.8
1935/39	13.6	14.6	12.6
1940/44	22.9	27.4	18.1
1945/49	16.8	22.1	11.3
1950/54	6.2	7.9	4.5

[1] In the ten-year period beginning 1925 the lines of boys and girls cross.

2. Trends of Mortality Rates during the Past Hundred Years

Records of the Central Bureau of Statistics made it possible to calculate mortality rates in adolescents since 1840 (Fig. 1, Table 1). Until 1860 the mortality curve fluctuates, probably as a result of epidemics. Since then it shows a decline which has continued for almost a hundred years up to the present moment, interrupted only by the two world wars.

In the First World War the total adolescent mortality increased from 26 per 10,000 in 1913 to 68 in 1918, thus reaching the same height as around 1850. The next few years showed a sharp decline and in 1924 the death rate was about as low as would have been expected if the war and the influenza epidemic had not intervened.

Similar trends existed during and after the Second World War: a marked increase from 13 per 10,000 in 1939 to 45 in 1945, thus reaching a level corresponding to that of around 1885. Then follows a sharp decline, with 1947 figures falling below the 1939 level. The increase in mortality rates during the Second World War was relatively much greater and of an entirely different character than that during the years 1914–1918 (§ 7).

A survey of the decline of adolescent mortality rates during the past hundred years shows a process suggestive of uniform *acceleration* rather than of uniform *speed*.

TABLE 2

Time for bisection of the mortality of adolescents.

Year	Mortality per 10,000	Interval (years)
1840/1844	68.9	
		60
1900/1904	36.0	
		30
1931	18.6	
		16
1947	10.7	
		7
1954	5.2	

As the above bisection table shows, the rate of decline accelerates increasingly.

TABLE 3

Recent trend of adolescent mortality per 10,000.

Year	Total	♂	♀
1950	6.9	8.9	5.0
1951	6.2	8.1	4.3
1952	5.5	6.8	4.2
1953[1]	7.2	9.1	5.2
1954	5.2	6.5	3.9
1955	5.4	7.2	3.6

[1] Victims of floods included.

The adolescent mortality rate now amounts to only 4–7 per 10,000 for this age group. This means that in a town of 20,000 inhabitants, among whom there are generally around 1800 adolescents, there is only one death per year of persons between the ages of 15 and 19 years.

These very low figures should not lead to the assumption that adolescent mortality is not liable to further reduction. The conclusion that medical care for adolescents has become superfluous is even less warranted.

3. Trends of Mortality according to Sex over the Past Fifty Years

In 1955 adolescent mortality had fallen to $\frac{1}{7}$ of the level of 1900, in boys to $\frac{1}{5}$, in girls to $\frac{1}{10}$. This greater decline in the mortality rates for girls than for boys has had the result that instead of an excess mortality for girls there is now an excess mortality for boys. About 1930 boy and girl

mortality was approximately the same and since then there has been an increasing excess mortality for boys, so that the mortality rates for boys during 1950/52 were even 1.8 times as high as those for girls. How is this reversal to be explained?

A shift in the significance of certain causes of death (especially tuberculosis and accidents) is closely associated with it. About 1920 tuberculosis was by far the leading cause of death in adolescents (half of the total mortality), whereas during 1953/54 it occupied the fifth place with 3 per cent of the total mortality (§ 4).

About $1\frac{1}{2}$ times as many girls as boys die from tuberculosis. It is evident that formerly the proportion between the mortality rates for boys on the one hand and those for girls on the other was far more influenced by this fact than is the case at present, now that tuberculosis mortality rates are hardly of significance any more.

Because these rates form a smaller percentage of the total adolescent mortality, the factor of accidents increases in importance: from 8 per cent in 1920 to 34 per cent during 1953/54. Accident-mortality among boys is far greater than among girls (approximately in a ratio of $3\frac{1}{2}:1$).

After deducting the mortality from tuberculosis and accidents from the total adolescent mortality, it appears that since 1900 an excess mortality among boys has occurred, which in the course of years has relatively increased. It is a general rule that for all causes of death—except tuberculosis and pertussis—mortality among boys is higher than that among girls.

Excess mortality among boys is not restricted to this particular age group, nor to The Netherlands alone. It also occurs in infants, pre-school children, and school children, and is also found abroad.

Martin, for example, found that in England and Wales the mortality rates among boys were considerably higher than those among girls. He, too,notices that for the past hundred years the excess mortality among boys has steadily increased, in other words, that mortality among girls has declined more rapidly than among boys. It is a general rule that as the mortality rates of a particular age group decrease, the excess mortality among boys increases (Herdan). As yet this fact has not been sufficiently explained. It is assumed that owing to their work and activities men and boys are more exposed to all kinds of risks, with regard both to accidents and infections.

This assumption does not explain the fact that even among babies there is an excess mortality among boys, and neither does it explain the excess boy mortality after elimination of accidents, nor the fact that excess mortality has increased in the course of the twentieth century, although girls are more and more being brought up in the same way as boys. In various publications the excess mortality among boys is reduced to genetical differ-

ences, environmental influences and differences in metabolism. The excess rates for males also in the adolescent age group seem, as yet, to be unexplained.

4. The Pattern of Causes of Death

In the course of years the nomenclature for the causes of death has been changed many times.[1] Moreover, diagnostic possibilities have shown a rapid development. How great the influence of these changes has been on the pattern of causes of death cannot be determined with certainty, but it is likely that the general trends have not been materially affected.

Not only has adolescent mortalilty sharply declined, but also the mutual relations between the causes of death have changed. A pattern of leading causes of death has been drawn up for a number of periods (Table 4).

It is evident that mortality from tuberculosis has declined far more sharply than the total adolescent mortality. Death from accidents has hardly declined at all (§§ 5 and 6, Fig. 2).

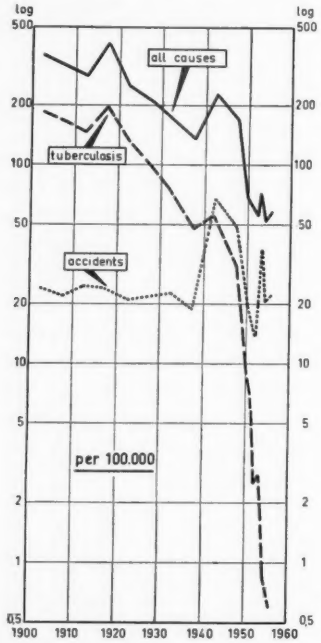

Fig. 2. Death rates of adolescents per 100,000, 1901/4–1955.

[1] For the classification of causes of death in different periods see: J. H. de Hass, *Atlas of Child Mortality in The Netherlands*. 1956.

TABLE 4

Five leading causes of death in adolescence in different periods.

A = % of total mortality; B = per 100,000.

	1908/10	A	B	1937/39	A	B
1	Tuberculosis	52	151	Tuberculosis	34	45
2	Accidents	8	23	Accidents	15	20
3	Respir. dis.	7	20	Respir. dis.	10	13
4	Infect. dis.	6	18	Neoplasms	7	9
5	Heart dis.	5	14	Heart dis.	6	8
	1950/52			**1953/1954[1]**		
1	Accidents	27	17	Accidents	38	21
2	Neoplasms	14	8	Neoplasms	18	10
3	Tuberculosis	9	6	Heart dis.	10	5
4	Heart dis.	7	5	Respir. dis.	5	3
5	Respir. dis.	6	4	Tuberculosis	3	2

[1] Victims of floods (February 1953) excluded.

Mortality from neoplasms seems to have increased up to 1938, but after that to have remained virtually stationary. As a result of the decline in total mortality, death from malignant neoplasms has relatively gained in importance. Up to 1940 mortality from infectious and respiratory diseases and influenza together was responsible for about 10 to 12 per cent of the total mortality, and afterwards it shows a slight decline.

Mortality from heart diseases also shows a slight decline which, however, has not kept up with the decline in the total mortality: the relative importance of heart diseases as a cause of death has for the past years increased a little.

The percentage of adolescents dying without known or stated cause of death, remained stationary up to 1940, which means that their number per 100,000 declined almost in the same proportion as the total mortality per 100,000 (from 8 during 1908/10 to 3 during 1937/39).

During the Second World War there was a sharp increase in the percentage of unknown causes up to 15 per cent of the total mortality for 1943/45, higher than in any other age group of children. For the last few years the group of unknown causes has been of the same numerical order as tuberculosis mortality.

There is a marked difference between mortality patterns for boys and girls: not only is tuberculosis mortality among girls greater than among

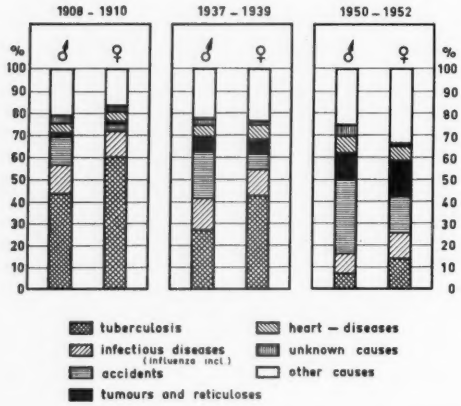

Fig. 3. Percentage distribution of causes of mortality in adolescence.

boys, but also the relative importance of this disease as a cause of death is greater among girls (Fig. 3). Meanwhile the importance of tuberculosis as a cause of death has greatly diminished for both sexes.

Since 1908/10 the percentage of the total mortality caused by accidents has become almost five times as large for girls and three times as large for boys. Accidents as a cause of death is of far less relative significance for girls than for boys (23 and 49 per cent respectively in 1955). In the course of the past fifty years there has been a shift in the order of significance of the causes of death among adolescents (Table 4).

In 1937/39 tuberculosis as a cause of death still came first, in 1950/52 it came second and in 1953/54 it came fifth; in 1955 it cannot anymore be considered an important cause of death for this age group. Since 1939 mortality from accidents and neoplasms has remained stationary. Their relative significance, therefore, has increased. The significance of respiratory diseases together with influenza and infectious diseases continues to decrease.

5. Tuberculosis

Deaths from tuberculosis among adolescents in 1952, 1953, 1954 and 1955 amounted to 20, 22, 7 and 5 respectively, i.e. only 2.5, 2.8, 0.9, and 0.6 per 100,000. If in 1955 tuberculosis mortality had been as high as it was in 1900, more than 1500 adolescents would have died from this disease, whereas actually there were only seven deaths.

Since the beginning of the century tuberculosis mortality has decreased almost 10 times as rapidly as the total adolescent mortality. Whereas a few decades ago tuberculosis was a dominant cause of death among adolescents, it now no longer plays a role as a cause of death at the "âge phtisiogène". This does not imply that this infectious disease at this age should no longer demand our attention. In 1954 more than 900 new cases were reported, a rate of 115 per 100,000. Yet, the morbidity too has greatly decreased for the last few years: as recently as 1949 more than 2100 new cases were reported, for a rate of 260 per 100,000. Over a period of five years morbidity decreased by nearly 60 per cent (de Haas, 1955).

During the two world wars the decrease in tuberculosis mortality was interrupted by increases of short duration (Table 5). The general trend of the decrease, however, has not been affected. Thus, in 1921 and 1946 the respective pre-war rates had again been reached. After 1946 the rate of decrease has accelerated: within 9 years' time tuberculosis mortality among adolescents fell from 33.9 in 1946 (compared to 44.2 in 1939) to 0.6 per 100,000 in 1955.

Before 1936 tuberculosis mortality among adolescents was higher by 20 per cent than among the whole population. This difference gradually became smaller until just before the Second World War the proportion was reversed. After 1945 adolescent mortality has decreased far more rapidly than the total mortality from tuberculosis, which in 1955 amounted to 5.5 per 100,000.

Until 1945 tuberculosis mortality among adolescents reflected the total mortality from tuberculosis fairly faithfully. This has no longer been the case after 1945.

Since 1900 tuberculosis mortality among girl-adolescents has constantly been higher than among boys: this difference seems to remain even for extremely low rates of mortality. A change is beginning to set in in the proportion of men and women dying from tuberculosis: at the beginning of the 20th century there was an excess mortality among women aged between 15 and 45, at present this is still the case in the age groups between 15 and 39 (van der Lee, van Heycop ten Ham).

6. Death from Accidents

In agreement with international usage death from accidents is defined as comprising all deaths resulting from external force: traffic accidents, burns and scalds, drownings, murder and suicide, immediate results of acts of war, and the like.

Whereas mortality from practically all other causes has decreased since

TABLE 5

Mortality from tuberculosis and accidents in adolescence 1900–1954, per 100,000.

Periods	Tuberculosis			Accidents		
	Total	Boys	Girls	Total	Boys	Girls
1901/04	186.5	166.7	206.5	24.0	39.6	8.4
1910/14	145.8	122.7	168.9	24.5	39.1	9.8
1920/24	136.0	109.3	157.4	20.7	34.2	7.1
1930/34	72.7	58.6	87.1	23.4	37.5	9.2
1940/44	56.0	51.3	60.8	68.1[a]	98.2[a]	37.1[a]
1945	67.9	66.7	69.1	159.2[b]	244.6[b]	71.3[b]
1946	33.9	32.7	36.2	29.8	50.2	8.5
1947	27.7	25.4	30.1	27.0	45.3	8.0
1948	16.3	15.8	17.1	19.8	30.4	9.2
1949	10.9	10.1	11.8	17.3	27.4	6.8
1950	9.2	8.0	10.6	20.8	32.7	11.1
1951	6.8	6.6	7.1	16.5	23.4	7.3
1952	2.5	1.9	3.1	14.5	22.7	5.9
1953	2.8	2.0	3.6	35.2[c]	47.4[c]	22.5[c]
1954	0.9	0.7	1.0	20.4	31.6	8.9
1955	0.6	0.5	0.7	21.8	34.1	9.0

a of which war casualties: 44.4, 61.5, 26.8.
b of which war casualties: 119.5, 182.6, 54.2.
c of which victims of floods: 13.8, 14.0, 13.7.

1900, death from accidents remained practically at the same level (Table 5). From 1900 to 1940 death-rates fluctuated around 20 per 100,000 (about 8 for girls, about 35 for boys). During the Second World War accidental death rose steeply to a peak of 160 per 100,000 in 1945. In 1947 the pre-war level had re-established itself, and after that date there has been a gradual decrease to 14.5 in 1952 (23 for boys, 6 for girls). During the past two years this low level has not been maintained.

Since the beginning of the twentieth century death from accidents among pre-school children has declined by one third: from 64 per 100,000 in 1908/1910 to 40 in 1950/52. The process was a gradual one. During the Second World War there was a rise, gradually subsiding to the pre-war level, which was reached in 1948 (van Gelderen). Accidental death among school children has not decreased for the past 50 years, but has been fluctuating around 20 per 100,000 (van den Berg and de Haas, 1955).

The pattern of the causes of accidental death among adolescents has changed (Fig. 4). In the period 1920/1922 (figures of earlier years cannot

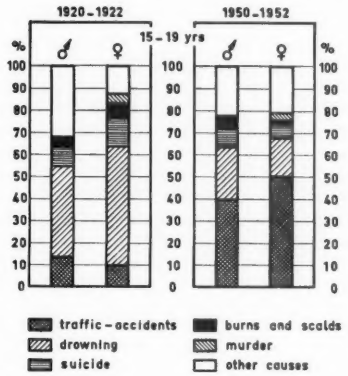

Fig. 4. Percentage distribution of causes of accidental death in adolescence.

very well be used for purposes of comparison) drowning was the commonest listed cause: 43 per cent (even 54 per cent for girls) of the total mortality from accidents. In 1950/52 traffic accidents ranked first, accounting for 42 per cent of the total (girls 50 per cent).

In the course of the years up to 1945 the relative significance of suicide remained practically the same: about 10 per cent of the total mortality from accidents, for a rate of 1 to 2 per 100,000 in this age group. Suicide is generally reported to decrease during times of war (Dublin). During the Second World War this decrease did not occur in the age group of 15 to 19 years in The Netherlands; there were, on the contrary, signs of a slight increase. After 1947 the number of suicides has decreased.

During the Second World War accidental death increased very considerably (Table 5). It stands to reason that the increase in accidental death was largely due to the immediate results of acts of war and to accidents with fire-arms. Those who lost their lives abroad in the services, in deportation, or as prisoners of war are not included in the surveys of the Central Bureau of Statistics.

During the war death from traffic accidents among adolescents greatly decreased as a result of reduced traffic. In 1945, as military traffic increased, the number of traffic accidents rose again.

The trends of death from traffic accidents among pre-school children were almost the reverse: for this group the rate increased during the war and then underwent a gradual decrease (van Gelderen). The general strain during the war inevitably led to a slackening of maternal care, from which young children suffered most. Death from traffic accidents among pre-

school children showed a sharp increase only in those countries immediately involved in the war.

Among school children death from traffic accidents remained unchanged during the war. Apparently the influence of reduced road traffic was counteracted by bad general conditions (van den Berg and de Haas, 1955).

For all age groups accidental death among boys is higher than among girls: for pre-school children about twice, for school children three times, and for adolescents almost four times as high. All divisions of the group "death from accidents" show an excess mortality among boys, including mortality immediately resulting from acts of war. In large scale natural disasters this difference does not occur: thus the floods of February 1953 in The Netherlands claimed as many victims among boys as among girls from 15 to 19 years, viz. 57 and 53 respectively.

Mortality as a result of the floods amounted to rates of nearly 14 per 100,000 (calculated for the whole country), i.e. nearly 20 per cent of the total mortality and nearly 40 per cent of the total accidental death among adolescents in 1953.

(For References and Summary see Part II of this article which is to be published in the March issue of *Acta Pædiatrica*.)

Correction

The summaries belonging to the article of L. I. Wolf & H. McC. Giles: Urinary Excretion of Amino-Acids and Sugar in the Nephrotic Syndrome. A Chromatographic Study (*Acta pædiat. 45:* 489, Sept. 1956) have been translated in an inadequate way. The French and German summaries should read as follows:

L'excrétion urinaire des acides aminés et des sucres au cours du syndrome néphrotique. Etude chromatographique.

L'élimination urinaire des acides aminés et des sucres a été étudiée chez 29 enfants néphrotiques par chromatographie sur papier. Une amino-acidurie a été trouvée chez 25 malades, et une glycosurie chez 16 malades. La chromatographie revêlait principalement deux types d'amino-acidurie : l'un montrait l'existence d'un déficit de la réabsorption tubulaire, l'autre peutêtre présentait un trouble du métabolisme des acides aminés associé avec un degré moin gros d'un déficit de la réabsorption tubulaire. Le prognostic était plus mauvais pour les enfants qui montraient une amino-acidurie du premier type.

Ausscheidung von Aminosäuren und Zucker im Urin bei Nephrose-Syndrom. Eine chromatographische Studie.

Der Urin von 29 Kindern mit nephrotischem Syndrom ist durch Papierchromatographie auf Aminosäuren und Zucker untersucht worden. Bei 25 Patienten wurde Aminoacidurie und bei 16 Patienten Glykosurie gefunden. Aminoacidurie kam vorherrschend in zwei Mustern vor, von denen eines auf eine Schädigung der tubulären Rückresorption hinwies, während bei dem anderen möglicherweise eine Störung im Aminosäurenstoffwechsel, verbunden mit einem geringeren Defekt der tubulären Rückresorption, besteht; die Prognose war schlechter für die Kinder, die das erste chromatographische Muster zeigten.

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